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Faculdade de Medicina Veterinária

COMPLICATIONS ASSOCIATED TO SUBCUTANEOUS URETERAL BYPASS (SUB) PLACEMENT IN CATS: A RETROSPECTIVE STUDY

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RESUMO

COMPLICAÇÕES ASSOCIADAS À COLOCAÇÃO DE *BYPASS* URETERAL SUBCUTÂNEO (SUB) EM GATOS: ESTUDO RETROSPETIVO

A obstrução ureteral é uma patologia cada vez mais frequente, especialmente em gatos, sendo a causa mais comum uma obstrução intraluminal secundária a ureterolitíase. O diagnóstico e maneio médio da obstrução ureteral deve ser feito de forma célere uma vez que pode induzir um rápido declínio da função renal assim como lesões irreversíveis do parênquima renal. A colocação de um *Bypass* Ureteral Subcutâneo (SUB) tem sido uma operação terapêutica crescente, constituindo um novo tratamento paliativo promissor.

Este estudo pretende descrever as potenciais complicações e prognóstico de gatos com diagnóstico de obstrução ureteral e submetidos à colocação de um dispositivo SUB num centro de referência da região parisiense, assim como detetar fatores que possam ter influenciado estes parâmetros. Foi efetuado um estudo retrospetivo com uma análise detalhada dos dados clínicos de 129 gatos nos quais foi colocado um SUB num centro de referência na área Parisiense.

As complicações graves identificadas consistiram em oclusão (n=41, 32%), mineralização do dispositivo (n=10, 8%) e extravasamento de urina do dispositivo ou do trato urinário (n=6, 5%). As complicações ligeiras descritas foram: sinais de disúria (n=38, 29%), bacteriúria (n=32, 25%) e anemia (n=25, 19%).

A nível temporal, as complicações graves foram identificadas em média 541 dias após a cirurgia e foram associadas à presença de letargia e oligúrio-anúria aquando da admissão hospitalar. Já as complicações ligeiras, estas foram observadas 148 dias após a cirurgia, com uma associação a anorexia ou disorexia prévias à hospitalização assim como a um historial de doença renal crónica. A realização de uma segunda ou mais cirurgias foi associado tanto com complicações graves como ligeiras.

A taxa de mortalidade do presente estudo foi de 19% mas esta não se correlacionou com complicações ou com qualquer outro parâmetro testado, sugerindo assim que, o prognóstico de após intervenção continua incerto.

Em suma, os resultados do presente estudo sugerem que a colocação de um dispositivo SUB é um tratamento viável de obstrução ureteral em gatos, com reduzidas complicações a curto e longo prazo, quando comparado com os *stents* ureterais e cirurgias ureterais tradicionais. Apesar da dificuldade em identificar fatores de prognóstico, os resultados deste estudo demonstram que, gatos com obstruções ureterais podem ter um bom prognóstico após a colocação de um dispositivo SUB.

Palavras-chave: Obstrução Ureteral, Ureterolitíase, Gato, *Bypass* Ureteral Subcutâneo, Complicações

ABSTRACT

COMPLICATIONS ASSOCIATED TO SUBCUTANEOUS URETERAL BYPASS (SUB) PLACEMENT IN CATS: A RETROSPECTIVE STUDY

The ureteral obstruction is becoming more frequent pathology, especially in cats, with the most common cause being an intraluminal obstruction secondary to ureterolithiasis. The diagnosis and medical management of ureteral obstruction should be made early as it may induce a rapid decline in renal function and irreversible lesions on the renal parenchyma. The placement of a Subcutaneous Ureteral Bypass (SUB) has been an increasing therapeutic option, considered as promising palliative treatment.

This study aimed to identify potential complications and outcome of cats with a diagnosis of ureteral obstruction and submitted to the placement of a SUB device in one referral center in the Paris area, as to detect factors that may had an influence in these parameters. A retrospective study was performed with a detailed analysis of the medical records of 129 cats submitted to the placement of a SUB device in one referral center in the Paris area.

The major complications identified consisted in occlusion (n=41, 32%), mineralization of the device (n=10, 8%) and urine leakage from the device or urinary tract (n=6, 5%). The minor complications described were: dysuria (n=38, 29%), bacteriuria (n=32, 25%) and anemia (n=25, 19%).

Major complications were seen a mean of 541 days after the surgery and were associated with the presence of lethargy and oligo-anuria at hospital admission. In the other hand, minor complications were observed 148 days after the surgery and were associated with anorexia or dysorexia at the hospital admission and a history of chronic kidney disease. The need for a second or more surgeries was significantly associated with both minor and major complications. The overall mortality rate of the present study was 19% but this was not associated with complications or other parameters tested, suggesting that, the prognosis after the intervention remains uncertain.

In summary, results of the present study suggest that the placement of a SUB is a viable treatment of ureteral obstruction in cats, with fewer short and long-term complications when compared with ureteral *stents* and traditional ureteral surgery. Despite the difficulty to identify prognostic factors, the results of this study demonstrate that, cats with ureteral obstruction could have a good prognosis after a SUB device placement.

Key words: Ureteral obstruction, Ureterolithiasis, Cat, Subcutaneous Ureteral Bypass, Complications

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LIST OF ABBREVIATIONS

ACVIM – American College of Veterinary Internal Medicine

ARF- Acute renal failure

AST – Antimicrobial susceptibility testing

BUN – Blood urea nitrogen

CASFM – Antibiotic Committee of the French Society of Microbiology (*Comité de l'antibiogramme de la Société Française de Microbiologie*)

ChuvA – *Centre Hospitalier Universitaire Vétérinaire d'*Alfort

CHV-Frégis – *Centre Hospitalier Vétérinaire* Frégis

CKD – Chronic kidney disease

CPR – Cardiopulmonary resuscitation

CRI – Constant rate infusion

CRRT – Continuous renal replacement therapy

CT – Computerized tomography

GFR – Glomerular filtration rate

IRIS – International Renal Interest Society

ISCAID – International Society for companion animal infectious diseases

MDR – Multidrug-resistant

MET – Medical expulsive therapy

PDR – Pandrug-resistant

RSS – Relative supersaturation

SDMA – Symmetric dimethylarginine

SUB – Subcutaneous ureteral bypass

Tetra-EDTA – Tetrasodium ethylenediaminetetraacetic acid

UPC – Urine protein creatinine ration

USG – urine specific gravity

UVJ – Ureterovesicular junction

XDR – Extensively drug-resistant

1. DESCRIPTION OF THE TRAINEESHIP ACTIVITIES

The trainee completed two traineeships. The first externship was in the *Centre Hospitalier Vétérinaire* Frégis (CHV-Frégis), in Arcueil-France and the second was at the *Centre Hospitalier Universitaire Vétérinaire d'*Alfort (ChuvA), situated in Maison Alfort-France.
The curricular externship was performed in the CHV-Frégis, under the supervision of Dr. Julie Lemétayer (Dipl. ACVIM). It lasted from 1/10/18 until 28/01/19, with a total duration of 4 months, reflecting approximately 756 hours.
The externship at the ChuvA was a 2 month-long extracurricular externship, which began on the 4/02/19 and lasted until 5/04/19, in a total of 385 hours, under the supervision of Dr. Celine Robert. Overall, the externship lasted 6 months, counting a total of 1141 hours of practical activities.

Traineeship at the CHV-Frégis

The first 2 months in the CHV-Frégis were spent in the Internal Medicine service and the last 2 months in the Surgery department. In both services two daily medical rounds happened, one as the day started and the other at the final of the day. Before those rounds, general examination to each hospitalized animal was performed by the trainee and the intern. In these rounds, all hospitalized animals were presented by the responsible clinician and an elaboration of a differential diagnosis list as well as complementary exams, surgeries and treatments were discussed. These medical rounds were attended by the day-time and night-time intern, senior clinicians, residents, board-certified specialists, nurses and trainees.
In the Internal Medicine service, both the trainee the intern conducted complementary exams and some treatments. The activities performed included: biochemical and urinary analysis, collection of blood samples, measurement of blood pressure, packet cell volume, electrocardiograms performance and reading, insertion of vascular and urinary catheters, nasoesophageal feeding tubes, collection of urine through cystocentesis and blood type typification. Besides that, the trainee assisted in the positioning of patients for ultrasonographical examination, both abdominal and cardiac, management of fluid therapy, drug administration and blood transfusions. The trainee had the opportunity to work in emergency cases and assist cardiopulmonary resuscitation (CPR). Occasionally, the trainee had the chance to assist to interventions such as gastrointestinal endoscopies, rhinoscopies, transtracheal/bronchoalveolar washes, bronchoscopies, enemas and thoracocentesis.

In the surgery service, the trainee and the intern aided the head nurse in the administration of pre-medications, complementary exams, management of fluid therapy and bandages and wound management. Afterwards, the trainee helped in the preparation of animals for surgery namely by preparing the anesthesia and pre-medication, administering the drugs, intubating the patient, doing the asepsis of the surgical field and transferring the animal into the surgical table. In all surgeries, the position of second hand surgeon was held by the trainee in alternation with the intern. Therefore, the trainee was able to participate in multiple soft tissue surgeries and the most frequent were: laparoscopic ovariectomies, brachycephalic surgery and palatoplasty with a CO_2 laser, removal of intestinal foreign bodies, cystotomy procedures, hepatic lobectomies, mastectomy, placement of a SUB device, gastric *volvulus*, diaphragmatic and perineal hernias. Other more unusual surgeries assisted were: cesarean sections (and respective neonatal reanimation), correction of patent *ductus arteriosus*, thoracotomies, thoracoscopies, pericardectomies, ligation of portosystemic shunts, repair of the hard palate cleft, total ear canal ablation, unilateral arytenoid cartilage lateralization, correction of chylothorax and ectopic ureters.

The trainee also assisted in orthopedic and neurologic surgeries such as total hip replacements, tibial plateau leveling osteotomies, trochleoplasties, tibial tuberosity transpositions, arthroscopies, laminectomies, corpectomies and fracture corrections. The short-term postoperative care was mainly conducted by the trainee and the intern, under supervision of a senior clinician. Once again, if there was free time between surgeries, the trainee could go and attend consultations, which helped her to understand the entire path that leads to a surgery and to further discuss it with the senior clinician.

In both services, most of the days had moments of debate and discussion, in which the author and senior clinicians would discuss a multitude of cases. The trainee could also go and attend consultations with high graduated clinicians, which was an opportunity to debate differential diagnoses, diagnostic and treatment plans, as well as to develop critical thinking skills.

Every Friday morning, the trainee went and assisted to continuous practice education given by senior clinicians. These lectures were integrated in the hospital routine in order to support a continuous formation of their clinicians with the most recent advances in veterinary medicine.

Traineeship at the ChuvA

The externship at the ChuvA was based on weekly rotations, and the services attended were: Dermatology, Preventive Medicine, Reproduction, Surgery, Convenience Surgery, Internal Medicine, Ophthalmology, Neurology, Cardiology, Exotic Animals, Physiotherapy and Rehabilitation.

The trainee individually received each animal and did an initial pre-consultation. The pre-consultation started by taking the medical history, performing a general clinical examination and, when needed, an orthopedic or neurologic exam along with basic laboratory testing. Afterwards, the trainee presented the case to the responsible clinician, with a list of differential diagnoses and proposing justified complementary exams, in order to reach the definitive diagnose, as well as an appropriate treatment plan. Following the consultation, it was responsibility of the trainee to ensure that all complementary exams and procedures were performed and to write the clinical report. At the end of the day, the team discussed clinical cases and some topics were further debated in small lectures given by senior clinicians.

The first week was carried out in the service of Preventive Medicine, where the trainee learnt about some of the legislation and vaccination plans of the country. The trainee had the responsibility of choosing the most suitable plan to the animal, fill in passports, introducing the electronic identification and prescribe accurate anti-parasitic treatment.

In the second week, in the service of Reproduction, the trainee had the chance to assist to artificial inseminations, collection of semen samples, gestational echographies and monitoring reproductive cycles.

Afterwards, in the service of Internal Medicine, the trainee was exposed to several cases, which were amply discussed with clinicians. In the pre-consultation, the trainee was responsible to guide and accompany the animal when there was the need of hospitalizations, radiographic or echographic exams.

In Ophthalmology, it was requested to the trainee to perform fundoscopic exams, Schirmer tests, fluorescein tests, reflexes tests, amount other.

In Cardiology, the trainee assisted to various echocardiographic exams and electrocardiograms, had clinical discussions about treatment plans and attended lectures given by board-certified specialists.

Regarding the Neurology department, the trainee had to perform detailed neurologic exams and interpret its results to provide a list of differential diagnoses.

Concerning the Exotic Animals service, pre-consultations were performed both in small mammals and birds. Moreover, the clinicians held lectures about the most common diseases in these animals, which were attended by small groups of students.

In the Surgery service, the trainee did pre-consultations in which she performed orthopedic and neurologic exams when needed. Furthermore, she had the opportunity to discuss diagnoses and surgical approaches with the responsible clinician. In the Convenience surgery service, the trainee had the opportunity to perform sterilizations and castrations of cats as a first hand surgeon. The animal was the trainee's responsibility since the pre-consultation, during the anesthetic induction, the surgical procedure until the postoperative management. Moreover, the trainee assisted to other surgeries such as cesareans sections (and respective neonatal reanimation), total ear canal ablation, pyometras and correction of a vaginal hyperplasia. The students also attended sessions of physiotherapy and rehabilitation such as hydrotherapy, electric stimulation and massages

Lastly, the trainee spent her last week in the Dermatology service where she collected skin and fur samples which were afterwards analyzed. There was also the opportunity to attend small lectures given by board-certified specialists and to participate debates.

2. BIBLIOGRAPHIC REVIEW

2.1 Urinary system anatomy

The kidneys and ureters are in the retroperitoneal space. The kidneys are paired, bean-shaped structures and each of them has a cranial and caudal pole and a ventral and dorsal aspect. The right kidney is firmly attached and associated with the renal fossa of the caudate liver lobe. The left kidney is generally more mobile and lies more caudally than the right kidney (Lanz & Waldron, 2000).

The hilus is located in the medial aspect, where the renal artery, nerves and lymphatic vessels enters and the renal vein and ureter exit (Tobias & Tillson, 2018). Blood supply to the kidneys comprise approximately 25% of the cardiac output. It has been reported that 10% of cats have multiple renal arteries supplying the kidneys, especially the left kidney. This is particularly important when considering nephrotomy or nephrectomy (Christie, 2003).

The kidney is composed of an outer cortex and an inner medulla. Externally, there is a fibrous capsule that is surrounded by adipose tissue, which can make gross evaluation of size difficult, especially in obese animals. The urine flows to the renal pelvis through the collecting ducts and is evacuated by the ureter (Tobias & Tillson, 2018).

The ureters are fibromuscular tubes that transport urine from the renal pelvis to the urinary bladder. They course caudomedially along the psoas major and minor muscles. The left ureter runs laterally to the aorta, while the right ureter is lateral to the caudal vena cava, until both ureters turn ventrally to the urinary bladder after passing the extern iliac vessels (Adams, 2017). In a small portion of animals, the ureters (more commonly the right ureter) is abnormally deviated medially and crosses the caudal vena cava dorsally which results in a retrocaval or circumcaval ureter (Cornillie, Baten & Simoens, 2006; Doust, Clarke, Hammond, Paterson & King, 2006).

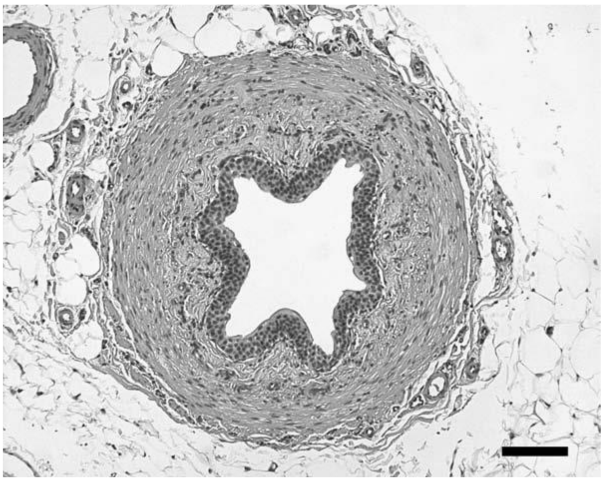
Between the ureteral openings in the urinary bladder wall and the proximal urethral opening in the urinary bladder neck there is a region named the trigone (Lipscomb, 2018). Just before entering the urinary bladder in the trigone region, the ureters recurves slightly, resulting in a j-shaped conformation. Then, they run obliquely within the urinary bladder wall resulting in a valve-like effect called the vesicoureteral valve. This promotes a unidirectional flow of urine that prevents the reflux of urine to the kidneys (Adams, 2017).

The length and diameter of ureters vary among species and breeds. The normal diameter of the feline ureter's lumen has been reported to be between 0.3 to 0.4mm. This is a predisposing factor for ureteral obstruction (Hardie & Kyles, 2004; Berent, Weisse, Todd & Bagley, 2014).

With fluid diuresis these values can increase but normally the maximum ureteral luminal diameter is less than 2.7mm (Adams, 2017).

The ureters are composed of an inner mucosal layer, constituted by a transitional cell epithelium and the lamina propria, several layers of smooth muscle and an outer adventitial layer, as seen in figure 1. The lumen is normally collapsed and opens only when the bolus of urine passes through. In the urinary bladder, the mucosa continues through the wall, but the muscle layer is replaced by the attachments of the detrusor muscle (Hardie & Kyles, 2004).

Figure 1. Section of a normal ureter from an adult cat (adapted from Hardie & Kyles, 2004).



The urinary bladder, composed by an apex, a body and a neck, lies within the peritoneal cavity and is attached to the abdominal wall by the median ligament and the lateral ligament. The median ligament is ventral and can be cut before cystostomy while the lateral ligaments contain fat along with the distal portion of the ureter (Lipscomb, 2018).

The urinary bladder is constituted by an outer serosa, the detrusor muscle and the urothelium, with consists of a transitional cell epithelium and the submucosa. The interdigitating fibers of the detrusor muscle are continuous with the smooth muscle of the urethra, which means that there is no anatomically distinct internal sphincter at the vesicourethral junction (Lipscomb, 2018).

2.2 Physiology

The kidneys have an important role in maintaining the homeostasis. They regulate the volume and composition of extracellular fluid by producing urine. They respond to water, electrolyte, and acid-base disturbances by specifically altering the rate of reabsorption or secretion of these substances. In addition, they have a number of endocrine function and are integral in the regulation of the systemic blood pressure and in the red blood cell production (Valender, 2013). The basic functional unit of the kidney is the nephron. The nephron is composed by the renal corpuscle, where the blood is filtered forming the ultrafiltrate, and by the renal tubules, where some filtered substances are reabsorbed and some plasma components are secreted. The volume of ultrafiltrate formed is primarily determined by the functional renal mass but it is also affected by the hydrostatic pressure within the glomerular capillary tuft (Valender, 2013).

Normally, water and solutes are freely filtered while all the cellular components and plasma proteins with the size of albumin are retained in the bloodstream. Substances with a molecular radius of 4 nm or more are not filtered whereas molecules with a radius of 2 nm or less are filtered without restriction. However, the net electrical charge of a molecule also affects his filtration's rate, the cationic form of many substances being more freely filtered than the neutral form which is itself more freely filtered than the anionic form of the same molecule (Valender, 2013).

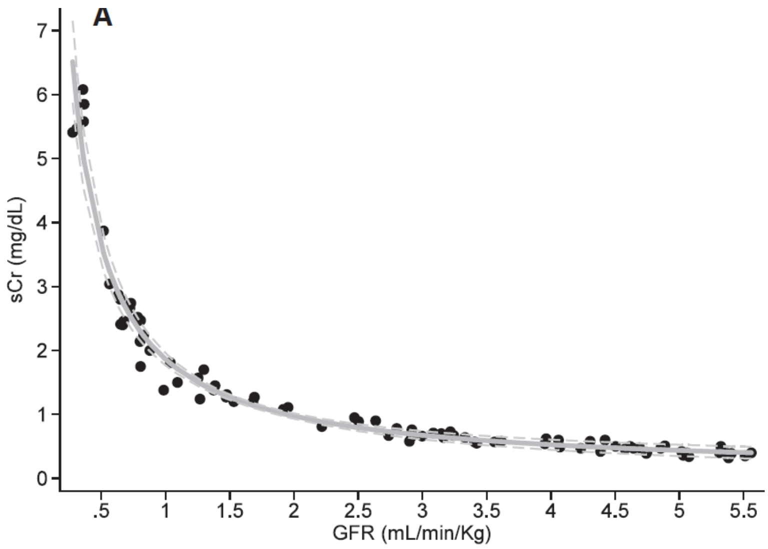
The majority of the ultrafiltrate formed in the glomerulus is reabsorbed by the renal tubules rather than excreted in the urine. Thus, there is a reabsorption of most filtered water and solutes as Na^+, Cl^- and $HCO3^-$, appearing only in minimal quantities in the urine and a complete reabsorption of the glucose and amino acids, that are not normally found in the urine besides at high filtered rate (Valender, 2013).

Substances that need to be eliminated by the urine, as urea and creatinine, are very poorly reabsorbed which results in an important excretion. The same occurs to exogenous substances and drugs, the reabsorption almost do not exist and furthermore, these substances are actively secreted into the tubular fluid, resulting in a high excretion rate (Valender, 2013).

2.3 Evaluation of the renal function

Azotemia is defined as a concentration of nitrogenous waste products in the blood above their reference intervals, which generally happens when 75% or more of the nephrons become non-functional. When adverse clinical manifestations are present in a more severe azotemia, the term uremia is used, to describe this clinical syndrome (MacPhail & Fossum, 2019). It is important to not just look for values outside the references intervals but understand that small changes in BUN (blood urea nitrogen) and/or creatinine concentrations may indicate significant pathology since those abnormal values are normally seen later in disease, as illustrated in figure 2 (Palm, 2017).

Figure 2. Correlation of the serum concentration creatinine and the GFR (adapted from Nabity et al., 2015).



Animals with a renal azotemia have a compromised urine concentration ability, with urine specific gravity (USG) values less than 1.035 in cats. Many cats with chronic kidney disease (CKD) present USG values between 1.006 and 1.020 and, in advanced stages of CKD, it is common to find isosthenuria, with USG values between 1.008 and 1.012. Despite all of this, some cats with CKD may preserve a substantial urine concentration ability (Polzin, 2017).

The glomerular filtration rate (GFR) is a clinically useful measure of the renal function and most frequently kidney diseases are diagnosed when GFR decreases with subsequent decrease excretion of renal biomarkers, leaving the animal azotemic (Palm, 2017). The determination of the GFR is the gold standard for measuring the renal function but due to its complexity and costs, other renal biomarkers have been used as an indirect measure of the GFR, even if early decreases in the GFR are not recognized by those indicators (Hall, Yerramilli, Obare & Jewell, 2014). Despite this insensitivity, the most commonly measured biomarkers are BUN and creatinine, but they represent only a fraction of the molecules that undergo decreased excretion in azotemia (Palm, 2017).

Urea is a nitrogen-containing compound and BUN is the measure of the amount of nitrogen urea in the blood (Palm, 2017). Urea is synthesized in the liver from the amino acids derived from the catabolism of exogenous and endogenous proteins. It is freely filtered at the glomerulus however, it can be reabsorbed from the renal tubules, and this occurs to a greater extent at slow tubular flow rates. Therefore, BUN is not a reliable indicator of GFR. Furthermore, production and excretion of urea is not constant. Serum creatinine is often used as a more reliable measure of GFR than BUN in patients with CKD (Ghys et al., 2014).

Furthermore, extrarenal factor may increase the urea concentration such as gastro intestinal hemorrhage, clinical conditions which increase catabolism as starvation, infection, fever, and some drugs, such as glucocorticoids. A diet with high protein intake can also increase BUN concentration, so a 12-hour fast is recommend before measuring BUN concentration. In this situation, a concurrent increase in serum creatinine concentration may not occur (DiBartola & Westropp, 2014).

Extra renal factors that can decrease the BUN concentrations are a low protein diet, a malabsorption, urea cycle enzyme deficiencies, iatrogenic overhydration and diseases that prevents water removal or causes a polyuria and polydipsia, such as hyperadrenocorticism and diabetes insipidus (DiBartola & Westropp, 2014; Palm, 2017).

The measurement of the creatinine serum concentration is generally preferred to the urea, as the concentration of the creatinine appears to be less affected by extra renal factors than the urea (Le Garreres, Laroute, De la Farge, Boudet, Lefebvre, 2007). The creatinine has many features that make it a good marker of the GFR. It is produced at a constant rate from creatine in muscle, it is then is distributed homogeneously throughout body water and finally, in the nephron, where it is freely filtered without any significant reabsorption or secretion (Watson et al., 2002). However, extra renal factors can influence the serum creatinine concentration. Since creatinine is produced in the muscle, a decrease in muscle mass can cause a decrease in serum creatinine, which is the case of pediatric, geriatric and cachectic animals (Braun, Lefebvre & Watson, 2003). The cats' breed also influence the serum creatinine concentration (Reynolds et al., 2010) and, additionally, a gradual increase is noted from new born to adulthood (DiBartola & Westropp, 2014; Palm, 2017). In addition, there is also an effect of food: animals fed with a meat-based diet have higher concentrations of serum creatinine until 12 hours after the meal, suggesting that blood samples should be collected when the animals are fasted (Watson et al., 2002).

Concentration of SDMA (Symmetric dimethylarginine) has been shown to be increased in cats with CKD and it strongly correlates with an increase in serum creatinine concentrations and a decrease in the GFR, revealing itself a new promising endogenous marker of GFR (Nabity et al., 2015). SDMA is a byproduct of protein methylation that is released into blood and eliminated primarily by renal clearance (<90%) with minor extra-renal influences. Studies have demonstrated that SDMA increases when there is a 25 to 40% decrease in GFR and, therefore, detects a loss on renal function earlier than the traditional measurement of creatinine (Hall et al., 2014; Nabity et al., 2015; Ernst et al., 2018). An elevation of the serum SDMA concentration above the normal reference interval was evidenced a mean of 14.6 months before the elevation of creatinine (Haall et al., 2014). However, similar to creatinine, SDMA needs to be interpreted in light of hydration status and physical examination findings but contrary to creatinine, SDMA is not affected by muscle mass (Hall et al., 2014; Nabity et al., 2015; Ernst et al., 2018).

Cystatin c is a proteinase inhibitor that is also gaining interest as a new renal marker. Its potential in Veterinary Medicine has been showed in some studies (Wehner, Hartmann & Hirschberger, 2008; Ghys et al., 2014). This protein has many of the properties required for an ideal endogenous GFR marker: a constant rate production, a freely glomerular filtration (because of the absence of plasma protein binding), no tubular reabsorption without catabolism and no extrarenal clearance (Séronie-Vivien et al., 2008; Ghys et al., 2014). In addition, a low intraindividual variability has been showed, and, the measurement of this protein is easy to realize, resulting interesting for the clinical use (Ghys et al., 2014). Despite the lack of studies, work developed by Wehner et al. (2008) demonstrated that cystatin c had a stronger correlation with the exogenous creatinine plasma clearance (r=0.63) compared with serum creatinine (r=0.57). Sensitivity for detecting reduced GFR was higher for serum cystatin c (76%) than for serum creatinine (65%), yet the serum creatinine had a slightly better specificity (91%) than serum cystatin c (87%). The same study showed that nonrenal diseases (such as neoplasia and infection) did not influenced the serum cystatin c concentration. Although these results seem promising, further investigations are required for the cystatin c to become an adequate biomarker (Wehner et al., 2008).

A compromised renal function may lead to multiple hematological and biochemical abnormalities. Phosphorus is excreted primarily via the kidneys so if dietary intake remains in a constant rate, a decline in the GFR will lead to his retention and, consequently, to hyperphosphatemia. Compensatory decrease in tubular reabsorption maintains a serum phosphorus concentration regulated in the early stages of CKD. However, when this compensatory adaptation reaches its limit, typically when GFR declines below 20%, the serum concentration of phosphorus starts to increase (Polzin, 2011). Low levels of potassium are also frequently associated with cats with CKD but are uncommon in dogs (Polzin, 2011). Levels of serum calcium can either increase or decrease, yet classically animals with CKD present a hypocalcemia (Barber et al., 1998). Indeed, ionized hypercalcemia was reported in 6% and ionized hypocalcemia in 26% in cats with spontaneous CKD (Barber et al., 1998).

The differentiation between acute renal failure (ARF) and chronic kidney disease (CKD) can be difficult but they must be discriminated at the moment of diagnosis because they differ in therapeutic and prognostic implications, since CKD is generally an irreversible disease while ARF has the potential to be reversible. However, ARF and CKD may co-exist in some animals, which is called the acute on chronic kidney disease (Polzin, 2013).

The ARF is a clinical syndrome characterized by an abrupt increase in serum creatinine and BUN concentrations (azotemia) in the absence of chronicity. This ARF leads to a rapid decline in renal function with devastating effects if a treatment is not provided in an early phase (Langston, 2017). It is more preferable to take appropriate preventive measures in situations recognized in which ARF is likely to develop than to treat an established ARF. Frequently, the clinicopathologic abnormalities associated with ARF are more severe than those observed in CKD since most of the compensatory mechanisms that developed in CKD are not present in ARF (DiBartola & Westropp, 2014).

CKD is defined as structural and/or functional abnormalities of one or both kidneys that have been continuously present for 3 months or longer (Polzin, 2013). CKD typically causes a slow but inevitably progressive decline in renal function however the rate of this progression is not predictable (Hall et al., 2014). While no treatment can correct these irreversible kidney lesions, consequences and complications associated can often be ameliorated by supportive therapy and thereby slow the progression course of the CKD and successfully manage the disease for months or even years in some cats after the diagnosis (Polzin, 2013).

Nowadays, clinical practice guidelines for diagnosis, prognosis and managing of CKD are based on the stage of the disease. The International Renal Interest Society (IRIS) has proposed a system for staging CKD in dogs and cats based on serum creatinine and SDMA concentrations and a sub-staging system based on the magnitude of the urine protein creatinine ration (UPC) and blood pressure. The stage of the CKD is based on a least 2 measurements of the animal's serum creatinine but ideally these values should be determined over several weeks to confirm short-term stability of the kidney function. The UPC is determined after the confirmation that neither a urinary tract infection nor a hemorrhage is present and, ideally, it should be measured on the basis of at least 2 urine samples collected with a minimum of 2 weeks interval. Regarding the systolic blood pressure, this should be determined after multiple measurements in a calm animal and, preferentially, repeated on separate days. (IRIS, 2017).

On the other hand, ARF is classified in 5 grades based on creatinine concentration and is further sub-classified as non-oliguric or oligo-anuric patients; or cases requiring renal replacement therapy. Contrary to IRIS staging for CKD, the ARF grades represent a moment in the course of the disease and need to be reevaluated regularly, during hospitalization (IRIS, 2016).

2.4 Ureteral obstruction

Ureteral obstruction is a challenging disorder often requiring highly sophisticated diagnostic and therapeutic measures as well as unique surgical skills (Shipov & Segev, 2013). This disorder has been diagnosed more often all over the world, for the past decades (Kyles et al., 2005a; Osborne, Lulich, Kruger, Ulrich & Koehler, 2008). The increased number of cases may be explained by the use of new diagnostic imaging modalities and increase awareness of the severe consequences of ureteral obstruction (Osborne et al., 2008). These factors combined with the morbidity and mortality resulting of the traditional surgical techniques make the use of new interventional alternatives appealing (Kyles et al., 2005b).

2.4.1 Signalment

Ureterolithiasis is a major cause of ureteral obstruction in dogs and cats (Selgev, 2011). Urolithiasis is a multifactorial syndrome where familial, congenital or acquired pathophysiologic factors that progressively increase the risk of precipitation of excretory metabolites in the urine (Osborne et al., 2008).

Evaluation of breed, gender and reproductive status predisposition by Lekcharoensuk et al. (2000) showed that British Shorthair, Exotic Shorthair, Foreign Shorthair, Havana Brown, Himalayan, Persian, Ragdoll and Scottish Fold cats have an increased risk of developing calcium oxalate uroliths as well as male cats and neutered cats. On the other hand, magnesium ammonium phosphate uroliths (struvite) are more prevalent in Chartreux, Domestic Shorthair, Foreign Shorthair, Himalayan, Oriental Shorthair and Ragdoll cats as well as female and neutered cats. The same study demonstrated that cats between 7-10 years old are more likely to develop calcium oxalate uroliths while struvite uroliths seem more frequent in younger cats, with age between 4-7 years old.

The lifestyle of the cat is also a risk factor associated to urolithiasis since indoor cats have less physical activity and, consequently, a reduced water consumption and low urine debit, facilitating the urinary minerals to precipitate (Gomes, Ariza, Borges, Schulz & Fioravanti, 2018).

2.4.2 Etiology of ureteral obstruction in dogs and cats

A correct classification of the ureteral obstruction is essential since the treatment plan is different depending on the nature of the obstruction along with the animal's medical condition. Ureteral obstruction can be classified as acute or chronic, unilateral or bilateral, partial or complete, static or dynamic (Shipov & Segev, 2013). The more frequent obstructions are partial and unilateral, especially those induced by ureteroliths (Kyles et al, 2005a; Adams, 2017).

Concerning its etiology, ureteral obstructions may also be caused by congenital or acquired diseases. Although congenital causes are rare, it includes ureteral stricture (Pullium, Dillehay, Webb, & Pinter, 2000), ureterocele and segmental ureteral aplasia (Lamb, 1998). Despite the fact that, a circumcaval ureter by itself does not cause a ureteral obstruction, this condition may potentially induce a ureteral stricture, which may progress to obstruction. As a matter of fact, ureteral obstructions in cats with a circumcaval ureter were caused by a ureteral stricture in 40% of cases, while the remaining 60% of cases had a ureteral calculi (Steinhaus et al., 2015).

Concerning acquired causes, they are usually due to mechanical obstruction of ureters. This can result from an intraluminal obstruction, an intramural lesion or an extraluminal compression (Hardie & Kyles, 2004).

Intraluminal obstruction is the most common cause of ureteral obstruction in dogs and cats and is usually caused by ureterolithiasis. However, blood clots or other inflammatory debris may also obstruct the ureter, particularly in cats (Selgev, 2011).

Intramural causes include ureteral stricture, ureterocele, neoplasia, proliferative ureteritis and fibroepithelial polyps. Among those, ureteral stricture seems to be the most frequent cause of intramural ureteral obstruction. Strictures can have various origins: a previous ureteral surgery, calculi embedded in the ureteral mucosa or, as already mentioned, congenital (Shipov & Segev, 2013). Neoplasia can be primary or metastasic. Although rare in dogs and cats, reported primary ureteral neoplasia include fibropapilloma, leiomyoma, leiomyosarcoma and transitional cell carcinoma (Hardie & Kyles, 2004; Adams, 2017).

Extramural compression may occur from retroperitoneal space occupying lesions (as masses), circumcaval ureter (Adams, 2017), urinary bladder pathology or from accidental surgical ligation of the ureter during ovariohysterectomy (Selgev, 2011).

2.4.3 Pathophysiology

The physiologic response to ureteral obstruction is extremely complex and after the relief of the obstruction, changes continue to occur in the previously obstructed kidney. The development of adverse events on the kidney depend on the specie, age, degree of obstruction, duration and whether or not the obstruction is unilateral or bilateral (Hardie & Kyles, 2004).

The longer the duration of the obstruction, the greater the potential for progressive irreversible damage. Therefore, a complete and prolonged obstruction will lead to renal fibrosis and atrophy. For instance, in normal dogs, after 1 week and 2 weeks of obstruction the GFR is permanently diminished by 35% and 54%, respectively (Wen, Frokiaer, Jorgensen & Djurhuus, 1999). An acute situation has the potential to be reversible and these changes may not occur or be incomplete if the obstruction is treated in time. Yet a complete and bilateral obstruction may be fatal within 48-72 hours (Adams, 2017).

The obstruction increases immediately the ureteral and renal pelvis pressure which is consequently transmitted to nephrons. When the pressure is high enough, it is accompanied by a decrease in the renal blood flow and in local GFR while a compensatory increase in the contralateral kidney GFR occurs. Therefore, if the contralateral renal function is preserved, the animal is not expected to become azotemic and clinical signs, if present, are mostly pain related due to the stretching of the renal capsule. Due to the unspecific clinical signs, these episodes of unilateral ureteral obstruction often go unnoticed by owners. However, this compensatory mechanism may not occur in animals with pre-existing CKD (Shipov & Segev, 2013).

With time, a leukocyte influx into the ipsilateral kidney also occurs, leading to a fibroblast recruitment and activation that contributes to a development of an interstitial fibrosis or glomerulosclerosis (Wen et al., 1999). If the contralateral kidney function is preserved, the kidney undergoes a compensatory hypertrophy, which may result in the "big kidney, little kidney syndrome" (Selgev, 2011).

The mechanical obstruction also induce a secondary local inflammation, edema and spasm of the ureteral muscle which exacerbates the clinical presentation (Selgev, 2011). Furthermore, it is worth noticing that, a dynamic obstruction caused by ureteral spasm has the potential to resolve itself spontaneously (Selgev, 2011).

2.4.4 Uroliths composition

Determining the urolith composition is a useful tool, given that it is important to prevent a recurrence and some diets may be instituted in order to reach that goal (Bartges & Callens, 2015). In cats, the reported recurrence rate for ureteroliths is 40% (Kyles et al., 2005b) and from the recurrent uroliths, 3.5% of them had a different mineral composition compare to the initial episode (Albasan et al., 2009). Therefore, in interventions where ureteroliths can be removed, all uroliths should be analyzed to determine its mineral composition and, moreover, recurrent uroliths must be resubmitted (Bartges & Callens, 2015).

The most common feline uroliths types are struvite and calcium oxalate, both representing almost 90% of 94778 feline uroliths analyzed in the Minnesota Urolith Center (Osborne et al., 2008). The majority of uroliths submitted were composed of calcium oxalate (49%) and struvite (41%). Purine-based uroliths (urate and xanthine) represent approximately 5% of uroliths, with a relatively stable prevalence over the years. Of the totality of uroliths submitted, 5% were composed of "other substances", such like matrix and calcium phosphate (Osborne et al., 2008). However, these values are concerning uroliths from all urinary tract. In a study by Kyles et al. (2005a), 93 ureteroliths were analyzed, in which 98% contained calcium oxalate.

Hypercalciuria promotes the formation of calcium oxalate uroliths, and multiple causes may be involved, such as idiopathic hypercalcemia, primary hyperparathyroidism, neoplastic disease, increased bone demineralization and an impaired renal tubular reabsorption of calcium (Palm & Westropp, 2011; Milligan & Berent, 2019). In a study by Berent, Weisse, Bagley & Lamb

(2018), 21% of cats were diagnosed with an idiopathic hypercalcemia, at some time after the surgery. Certain medications may also promote a hypercalciuria including loop diuretics and corticosteroids, as well as dietary factors like an increased intake of calcium and vitamin D and urinary acidifiers diets (Milligan & Berent, 2019).

Relative supersaturation (RSS) is a risk index of crystallization and it is important in the urolith formation. Uroliths typically form in an oversaturated urine with respect to the minerals that precipitate to form that type of urolith (Lulich, Osborne, Carvalho & Nakagawa, 2012; Bartges & Callens, 2015). The crystallization risk may be assessed indirectly by the urine pH, USG and microscopic evaluation (Queau, 2019). An increased urine concentration as well as a reduced water consumption therefore predispose to calculi formation, since it leads to the stagnation of the urine and restrains the crystals elimination (Milligan & Berent, 2019).

The urinary acidifiers diets are typically employed for the dissolution and prevention of struvite uroliths, however, it may promote calcium oxalate crystalluria because of the release of calcium carbonate and calcium phosphate from the bone, resulting in hypercalciuria (Osborne et al., 2008; Palm & Westropp, 2011). However, the effect of urine pH remains controversial. Several studies about the effect of acidic urine on the RSS of calcium oxalate diverged, showing that the acidity may increase the RSS (Bartges, Kirk, Cox & Moyers, 2013) or maintain it (Queau et al., 2013).

A study conducted by Lekcharoensuk et al. (2001) evaluated the association between dietary factors and the occurrence of calcium oxalate and struvite uroliths. The results suggested that diets with high protein, sodium, potassium, moisture, phosphorus and magnesium decreased the risk of calcium oxalate uroliths. This study also reported that, cats fed with moderate calcium-containing diets, were less likely to form calcium oxalate uroliths when compared to cats fed with lower and higher concentrations of calcium. Therefore, this study revealed that restriction of dietary calcium is a risk factor for calcium oxalate urolithiasis, contradicting the opposite prevailing consensus. Further investigation is needed in order to evaluate the influence of dietary calcium in the formation of calcium oxalate. At last, the same study showed that, in order to minimize the formation of struvite uroliths, diets should be formulated to contain higher fat content and lower protein and potassium concentrations (Lekcharoensuk et al., 2001).

2.4.5 Ureteroliths distribution

The number and location of ureteroliths within the ureter is an important consideration when deciding for the most appropriate treatment, yet there is still a lack of veterinary literature regarding this subject. The identification of concurrent renal and cystic calculi is also essential in therapeutic decision. One study documented that, in addition to ureteral calculi, 62% of cats had renal calculi whereas 9% had cystic calculi (Kyles et al., 2005a).

Another study by Nesser, Reetz, Clarke & Aronson (2018) reported that ureteroliths were more frequently situated in the proximal and mid ureter than in the ureterovesicular junction (UVJ), both in cats with single and multiple ureteroliths. Additionally, also a correlation between ureterolith size and location has been evidenced, with larger ureteroliths associated with a more proximal ureteral location, which may be due to the small ureteral luminal diameter in cats. Furthermore, the UVJ is a very small region of the ureter, compared with the mid ureter, which may explain the reduced number of ureteroliths in this region (Nesser et al., 2018).

The position of a ureterolith can also quickly change within the ureter, either by a normograde movement towards the urinary bladder, or a retrograde movement. Therefore, ureteroliths position identified at one moment may not correspond to their current position (Nesser et al., 2018).

Future studies are required to further evaluate the anatomy of the cat's ureter, in order to determinate if there is a presence of another anatomic or functional narrowing leading to a more frequent calculi lodgment in some regions, as seen in humans (Nesser et al., 2018).

2.4.6 Anamnesis and clinical signs

The presentation of cats with ureteral obstruction varies substantially from one patient to the other and clinical signs may not be apparent unless a bilateral obstruction or a unilateral obstruction with combination with a compromised function of the contralateral kidney occurs. In some cases, the ureteral calculi can be an incidental finding during abdominal imaging for unrelated reasons (Shipov & Segev, 2013).

Clinical signs are generally nonspecific including weight loss, reduced appetite and lethargy (Kyles et al., 2005a). If the animal is severely azotemic, signs of uremia can occur, namely vomiting, anorexia, polyuria and polydipsia. Signs directly referable to ureteral obstruction can also be present namely hematuria, oliguria, anuria and abdominal pain (Selgev, 2011). On physical examination, pallor of the mucous membranes, dehydration, asymmetrical kidneys and abdominal pain may also be found (Berent, 2011). These clinical sign contribute to the difficulty to diagnose and provide strict therapeutic guidelines to this heterogeneous group of patients (Shipov & Segev, 2013).

2.4.7 Laboratorial abnormalities

A study conducted by Kyles et al. (2005a) reported that 83% of the cats diagnosed with ureteral calculi were azotemic, with serum creatinine and BUN concentrations significantly higher in cats with bilateral ureterolithiasis compared with cats with unilateral ureterolithiasis. However, 76% of the cats with unilateral ureterolithiasis presented with azotemia, indicating that the renal function of the contralateral kidney was also compromised (Kyles et al., 2005a). In the same study, 54% of cats had hyperphosphatemia, 35% hyperkalemia, 22% hypocalcemia and 14% hypercalcemia. Cats frequently had a normocytic normochromic anemia at diagnosis (48%) (Kyles et al., 2005a) and this was either due to an underlying CKD, chronic inflammation (as some cats may have had a concurrent pyelonephritis) or excessive blood sampling during previous hospitalizations (Shipov & Segev, 2013).

Urinalysis often does not provide specific information in ureteral obstructions but may reveal hematuria, pyuria, cylindruria, crystalluria and bacteriuria (Shipov & Segev, 2013). However, crystalluria is not a consistent feature of urinalysis in cats with uroliths since uroliths can be present without crystalluria and, when present, crystalluria may not accurately predict the urolith type (Labato, 2017). The urine samples should be analyzed as soon as possible to prevent a false positive crystalluria considering that changes in temperature and elapsed time between urine collection and urinalysis may induce crystalluria (Bartges & Callens, 2015). The value of pH may help predicting the type of urolith present since struvite, calcium carbonate and calcium phosphate are less soluble in alkaline urine while ammonium urate, silica and cysteine are less soluble in acid urine (Labato, 2017). Low-grade metabolic acidosis associated with aciduria increases calcium resorption from bone and therefore urinary calcium excretion. Furthermore, acidic urine may decrease the action of citrate and pyrophosphate as calcium oxalate inhibitors. Lastly, calcium is also less reabsorbed from the distal tubule when the urine is acidic (Labato, 2017).

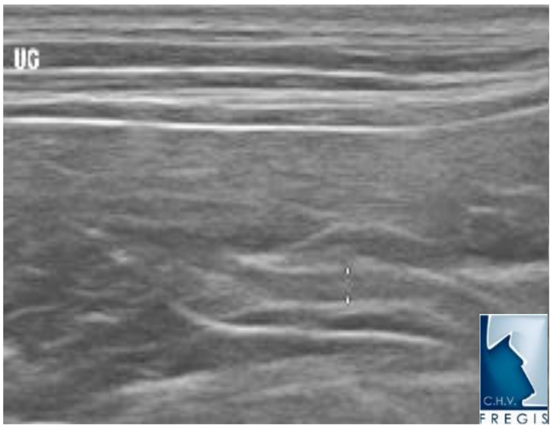
Bacteriuria was found in 25% of cats, with the most frequently isolated bacteria being *Escherichia coli* (Berent et al., 2018).

2.4.8 Imaging modalities

The diagnosis of ureteral obstruction in cats can be challenging and it is based on the history, clinical signs and laboratorial abnormalities, and is resorting to the use of imaging techniques to confirm the diagnosis (Selgev, 2011).

Ultrasonography is a useful tool to determine the degree of hydroureter, hydronephrosis and the exact location of ureteroliths, as seen in figure 3 and 4 (Lamb et al., 2018). It has the added benefit of allowing the clinician to assess to the renal geometry and architecture and it is a valuable tool when suspecting tissue lesions, such as strictures and neoplasia (Shipov & Segev, 2013). If a hydroureter is present without evidence of a shadowing ureterolith and with the peri-ureteral tissue hyperechoic, then a ureteral stricture should be considered (Zaid, Berent, Weisse & Caceres, 2011).

Figure 3 and figure 4. Abdominal ultrasonographies showing a hydroureter and ureteral calculi (original, kindly provided by the CHV-Frégis).

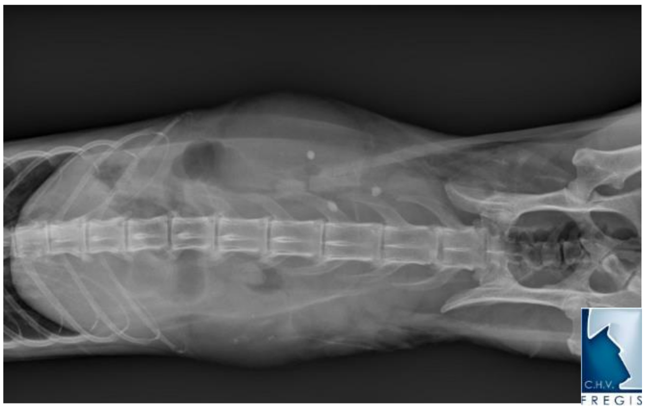


Legend: Left frame: ureter measuring 1.2mm with a hyperechogenic element of 1.3mm located in the mid ureter. Right frame: hyperechogenic element with an acoustic shadow.

Work developed by D'Anjou, Bébard and Dunn (2011) has shown that cats with clinically normal renal function not receiving IV fluids may have a pyelectasia reaching 3 mm. Nevertheless, the medians for maximal renal pelvic width were 1.6mm for cats with a clinically normal renal function and 2.3mm for cats with a clinically normal renal function with diuresis (D'Anjou et al., 2011). Knowing the exact diameter of the renal pelvis is a key piece of information, because it is important to decide which interventional option is best for each animal (Berent, 2011).

Radiographs, as showed in figures 5 and 6, are extremely useful to document uroliths size, number and location, since these are often underestimated with ultrasound (Berent, 2011). The radiopaque calculi that can be visualized with radiographs including calcium oxalate, struvite, apatite and silica while ammonium urate and cysteine are nonmineralized uroliths and thus not visible with radiographs, except if mixed with mineralized uroliths (Labato, 2017). However, ureteroliths smaller than 2 mm, which are common in cats, may be missed in the radiographs (Lulich & Osborne, 2008).

Figure 5 and figure 6. Dorsoventral and lateral view radiographs of a cat with bilateral ureteolithiasis (original, kindly provided by the CHV-Frégis).



The accuracy of survey radiography or ultrasonography for detecting feline ureteral calculi is only moderate, with false negative and false positive results recorded in both modalities. The sensitivity of radiography and ultrasonography for the diagnosis of feline ureteral calculi is estimated to be 81% and 77%, respectively, while the combination of both modalities increase the sensitivity to 90%, emphasizing the importance of combining these tools (Kyles et al., 2005a). Despite that, there is a good agreement between radiographic and ultrasonographic findings and discrepancies probably reflect moments in which calculi is present but not observed. Calculi may be missed ultrasonographically if the ureter cannot be adequately examined or missed radiographically if there is superimposition by other structures or if the calculi are not sufficiently opaque or large. In order to have a better visualization of the urinary tract, an enema is necessary in some patients (Lamb, Cortellini & Halfacree, 2018).

If ureteral obstruction is highly suspected but the obstruction cannot be evidenced using radiography or ultrasound, contrasts studies or computerized tomography (CT) could be considered (figure 7) (Etedali, Reetz & Foster, 2019).

Figure 7. Computerized tomography study of a cat with ureterolithiasis (adapted from Hardie & Kylies, 2004).

Legend: Transverse 5 mm sections of the abdomen of the cat were obtained. The CT slice shows a radiopaque calculi in the left kidney and proximal ureter (white arrow).

Intravenous excretory urography offers several advantages, providing information related to the renal vasculature, size and shape of the urinary tract. Although complications are rare, there are some reported cases of contrast medium-induced nephropathy by intravenous administration of the contrast material (Etedali et al., 2019). Furthermore, since the GFR is decreased in most cases of ureteral obstruction, there is a diminution of contrast elimination through kidneys and it may not be sufficient to make the diagnosis (Shipov & Segev, 2013).

Contrast CT scans are also useful for confirmation of the number and location of the ureteroliths, strictures, neoplasia or extramural compressive lesions, as well for distinction between partial and complete obstructions (Berent, 2011; Adams, 2017).

Alternatively, a percutaneous antegrade pyelography can be done to confirm a ureteral obstruction, when a sufficient pyelectasia is present. This technique provides good filling of the renal collecting system, regardless of the renal function, with a high sensitivity and specificity for the diagnosis of feline ureteral obstruction. The contrast is injected under ultrasonographic or fluoroscopic guidance, decreasing the risk of nephrotoxicity by avoiding systemic administration of the contrast. Before the contrast's injection, urine may be collected and sent for culture. Complications associated with this technique include leakage of contrast material, hemorrhage and blood clot formation (Etedali et al., 2019). Another option is a retrograde ureteropyelography, performed via cystoscopy and fluoroscopy, by injection of the contrast in the ureterovesicular junction (UVJ) with a retrograde progression of a higher concentration of the contrast's material (Berent, 2011).

2.4.9 Treatment

Ureteral obstructions require immediate care, in order to prevent a decrease in renal function, regardless of whether the obstruction is partial or complete (Lulich et al., 2016). The urgency and therapeutic intervention are determined by the nature of the obstruction (if it is static or dynamic), its location, presence and severity of clinic and laboratorial abnormalities (such as hyperkalemia) and the existence of urinary tract infection, while considering the risks associated with each one of the interventions (Kyles et al., 2005b). The clinician is challenged to consider more often less invasive alternatives. However, not all management strategies are appropriate for every animal or situation (Lulich et al., 2016).

2.4.9.1 Medical treatment

In cats with obstructive ureteroliths, a medical therapy should be considered as a first-line treatment for the relief of the obstruction. Nevertheless, medical treatment should not be continued in cats with progressive azotemia, persistently oliguric, anuria, hyperkalemic or with a progressive ureteral and renal pelvis dilatation (Lulich et al., 2016; Adams, 2017).

Medical dissolution may be applied in non obstructive uroliths, such as struvite, urate, cystine uroliths. Nevertheless, since the most common type of ureteroliths in cats is calcium oxalate, which are not amenable to medical dissolution, this therapy should not be attempted in cats arriving for medical care with an obstructive upper urinary tract urolith (Lulich et al., 2016).

Medical expulsive therapy (MET) may be part of the management of ureteroliths as an attempt to facilitate its passage by increasing the urine flow, while simultaneously monitoring the ureterolith's position and animal's condition (Adams, 2017). This medical therapy should be initiated immediately following the diagnosis, as a medical stabilization before a surgical procedure. Medical management should consist of aggressive intravenous fluid therapy with a close monitoring of the hydration status, electrolyte concentrations, body weight and possible cardiac disease, since it is not unusual for cats to become fluid overloaded (Berent, 2011). In addition, the use of an osmotic diuretic can be considered and, therefore, a constant rate infusion (CRI) of mannitol can be started, in cats without concurrent cardiac compromise (Berent, 2014; Lulich et al., 2016).

Other medical alternatives have been used with anecdotal reports of improvement in some cases and, consequently, drugs such as amitriptyline, prazosin and glucagon can be considered in addition to the MET (Berent, 2014; Lulich et al., 2016). In one report, amitriptyline has proved to be a potent, rapid and extremely effective blockade of the urinary smooth muscle contractions facilitating the passage of urethral plugs in cats, however there are no clinical reports supporting its use for ureteroliths (Achar, Achar, Paiva, Campos & Schor, 2003). In another study with 18 cats with ureterolithiasis, the administration of glucagon resulted in the movement of the urolith in only 4 cases. However, it was associated with a high number of side effects (Forman, Francey, Fischer & Cowgill, 2004). Pain management is also very important, to decrease the ureteral spasm (Berent, 2014).

Despite all of this, medical treatment for obstructive ureterolithiasis rarely result. Reported effective results occurs in only 8 to 13% of cases. Therefore, it is very important that owners are informed of this high rate of medical failure (Kyles et al., 2005b; Lulich et al., 2016).

When attempting for medical management, a risk for irreversible renal damage during the treatment should be considered, and this is one reason why medical management can only be applied for a very short period of time. Considering that the obstruction is frequently already present before the admission in hospital, this period of time may be even shorter to prevent irreversible damage. Since there is a high probability of recurrence of ureterolithiasis in cats, the benefits of potentially avoiding surgery must be weighed against the risks of the medical treatment and, above all, the renal function should be preserved (Shipov & Segev, 2013). Therefore, if the medical management fails over 24-72h, or the animal is not stable, presenting a hyperkalemia, overhydration, oliguria/anuria or a progressive hydroureter/hydronephrosis, an immediate renal decompression must be considered (Berent et al., 2014; Lulich et al., 2016). Nevertheless, intervention only should be considered if an experienced operator is available since a higher complication rate is associated with less experienced operators (Lulich et al., 2016). If an immediate resolution is not possible or the animal is too unstable, then the clinician can consider placing a nephrostomy catheter or initiate intermittent hemodialysis or a continuous renal replacement therapy (CRRT), when available (Berent et al., 2014).

Appropriate treatment of clinical signs and laboratory abnormalities should also be provided as necessary, such as antibiotic, antiemetic, among other (Berent et al., 2014).

2.4.9.2 Surgical treatment

2.4.9.2.1 Preoperative management

General anesthesia may be damaging for animals with a pre-existing renal disease since nearly every anesthetic agent causes a decrease in the GFR and renal blood flow. Consequently, measures should be taken in order to minimize any detrimental impact to the remaining renal function during surgery (Weil, 2010).

Before the general anesthesia, efforts should be made to reduce the level of azotemia, correct the dehydration, electrolyte disturbances as well as acid-base disorders, since, a high serum creatinine concentration and hyperkalemia at the preoperative period were found to be strongly associated with mortality after surgical correction of the ureterolithiasis (Mateo, Brodbelt, Kulendra & Alibhai, 2015). A careful evaluation of the fluid therapy of these animals is crucial, especially in anuric or oliguric cats who can become fluid overloaded. Anemia should also be identified and corrected if clinically needed before general anesthesia because it may potentially lead to a failure in the distribution of oxygen to tissues (Weil, 2010).

A potential for drug overdose may also occur since anesthetic drugs that are renally excreted could be affected by a decrease in renal excretion, making the selection of appropriate analgesic and anesthetic drugs and dosages, critical (Mateo et al., 2015). Release of catecholamine is produced in painful and stressful animal, which can lead to a decreased blood flow to the kidney. Therefore, a premedication with sedatives and analgesics can be very helpful in these animals. According to the guidelines from the International Society for Companion Animal Infectious Diseases (ISCAID), an antimicrobial prophylaxis with a 1st or 2nd generation cephalosporin is recommended, no more than 60 minutes before the surgery (Weese et al., 2019). For induction and maintenance of the surgery, propofol may be beneficial for cats with ureterolithiasis as it has minimal effects on the GFR (Weil, 2010). Isoflurane or sevoflurane may be used for maintenance, since these volatile anesthetics maintain an adequate renal blood flow (Weil, 2010).

The duration of general anesthesia should be minimized whenever possible, as a longer anesthesia time has been associated with hypothermia and the development of intraoperative complications (Redondo et al., 2012; Mateo et al., 2015; Deroy et al., 2017).). Hypothermia should be prevented by using various heating methods because it can lead to several negative consequences, including arrhythmias, coagulopathies and reduced oxygen delivery to tissues (Clark-Price, 2015). Hypothermia was the most common anesthetic related complication (93%), which is found especially in cats, due to its large surface area in relation to body weight (Luca, Monteiro, Dunn & Steagall, 2017). Hypotension is also a common consequence of a prolonged anesthesia, found in 82% of cats, which should be prevented since it may lead to hypoperfusion and, consequently, to a decreased renal blood flow and reduced GFR (Kulendra et al., 2014; Livet et al., 2017; Luca et al., 2017). Livet et al. (2017) reported a severe hypotension in one cat that ended up in euthanasia, the day after surgery. Therefore, in order to avoid this, it is essential to provide fluid therapy, as well as a judicious anesthetic monitoring with early management of intraoperative anesthetic related complications (Luca et al., 2017).

2.4.9.2.2 Traditional interventions

Renal decompression in cats may be realized traditionally, with procedures such as ureterotomy, ureteronephrectomy, ureteroneocystostomy and renal transplantation. However, these traditional interventions are associated with relatively high rates of complications and mortality, as well as persistent ureteral obstructions (Kyles et al., 2005b; Berent, 2011; Culp et al., 2016). The procedure performed depends on a multitude of factors, including the cause of the ureteral obstruction, location, presence of concurrent urinary tract illness and clinician preferences (Wormser, Clarke & Aronson, 2016).

A renal transplantation should be reserved for patients with irreversible azotemia and not necessarily for post renal azotemia caused by a ureteral obstruction (Berent, 2011).

It is also important to realize that a ureteronephrectomy is not an ideal treatment of feline ureterolithiasis, especially in cats with concurrent renal azotemia, because of the importance of preserving all renal function, whenever possible (Berent, 2011). Moreover, there is also a significant risk of recurrence of the obstruction in the contralateral kidney/ureter (Kyles et al., 2005b).

In a study conducted by Kyles et al. (2005b), where cats with ureterolithiasis were treated with traditional surgeries, there was a reported perioperative (since the recovery from anesthesia until 7 days after surgery) mortality rate of 18% and postoperative complications were described in 30% of cats. The traditional surgeries employed in this study included ureterotomy, ureteroneocystostomy, ureteronephrectomy and renal transplantation. An ureterotomy was preferred for removal of calculi in the proximal portion of the ureter, whereas an ureteroneocystostomy was more likely to be performed for a calculi presented in the distal portion of the ureter. The most common complications were urine leakage (16% and 15% for ureterotomy and ureteroneocystostomy, respectively) and persistent ureteral obstruction (3% and 11% for ureterotomy and ureteroneocystostomy, respectively). Despite these elevated rates, the surgeries were performed in 2 universities that had extensive expertise with ureteral surgery, consequently, higher morbidity and mortality rates may be found in clinics with less microsurgical experience.

A more recent study by Culp et al. (2016) evaluated the outcome of ureterotomy, reporting that only 78% of cats survived to hospital discharge and only 31% had a resolved azotemia after the surgery; and overall, postoperative improvement of laboratorial parameters was not as pronounced as it was for cats treated with ureteral *stenting*. Moreover, the most frequent complication was urine leakage, presented in 33% of cats, which leaded to a uroabdomen. These cats were significantly less likely to survive.

Other complications associated with these traditional surgeries include site edema, re-obstruction from nephroliths that pass to the surgery site, stricture formation and missed ureteroliths that are not removed (Kyles et al, 2005b; Milligan & Berent, 2019). Moreover, the ureteral surgery may result in a temporary postoperative obstruction of the ureteral lumen due to the mucosal edema at the ureterotomy site (Adams, 2017). It is crucial to ensure that all ureteroliths are removed, as some of small sizes may be difficult to palpate digitally during the surgery and may passed unnoticed, resulting in a continuous ureterolithiasis (Berent, 2011; Adams, 2017).

The presence of nephroliths could be a risk factor for reobstruction of the ureter since they have the potential to eventually pass into the ureter and obstruct it. Kyles et al. (2005b) reported that, 40% of cats had a recurrent ureterolithiasis within 2 years after the traditional ureteral surgery for the management of the initial ureteral obstruction and, 86% of these had evidence of nephrolithiasis on the initial imaging. However, cats which had already an episode of ureterolithiasis were probability more likely periodically evaluated by means of diagnostic imaging studies, whereas other cats may had undiagnosed episode of nephrolithiasis (Kyles et al., 2005b).

Therefore, in the opinion of Adams (2017), ureterotomy or ureteroneocystostomy should only be considered for the removal of solitary ureteroliths, without concurrent presence of ureteral stricture.

Given the potential complications and mortality associated with these traditional surgeries, alternatives have been investigated for animals over the past years. The ideal would be to find a less invasive technique that leads to an immediate renal decompression and stabilization of the azotemia while simultaneously preventing postoperative complications (Berent, 2011; Milligan & Berent, 2019).

2.4.9.2.3 Alternative interventions

Due to the small luminal diameter of feline ureters, available options for treatment are reduced, and ureteral *stents* and Subcutaneous Ureteral Bypasses (SUB) have been developed to overcome the limitations of traditional techniques for the management of ureterolithiasis in cats (Hardie & Kyles, 2004; Berent, Weisse, Todd & Bagley, 2014; Deroy, Rossetti, Ragetly, Hernandez & Poncet, 2017). Such devices are considered, by the consensus from the American College of Veterinary Internal Medicine (ACVIM) as first choice for the best possible outcome of obstructive ureteroliths in cats. Furthermore, fluoroscopic imaging, proper training and experienced operator are recommended, in order to optimize the animal's outcome (Lulich et al., 2016).

2.4.9.2.3.1 Ureteral *Stents*

Ureteral *stents* may be placed cystoscopically, by a percutaneously approach or open surgery. This is accomplished via pyelocentesis (normograde way), via cystotomy (retrograde way) or through an ureterotomy. In cats, most ureteral *stents* are placed surgically and using a normograde technique (Berent, 2011; Culp et al., 2016; Adams, 2017). Despite that, in some cases, ureterotomy was still required to allow the stent to pass through the obstructed region, leading to an increase risk for postoperative urine leakage at this site (Culp et al., 2016).

After the placement of ureteral *stents*, these permit the immediate passage of urine through the *stent* lumen (figure 8) and, over time, causes a passive dilatation of the ureter facilitating the passage of urine, crystals, uroliths and other debris through the ureter (Culp et al., 2016). This ureteral dilatation is also beneficial for cats with ureteral strictures (Berent, 2011).

Figure 8. Postoperative lateral view radiograph showing placement of a double-pigtail ureteral *stent* (adapted from Deroy et al., 2017).

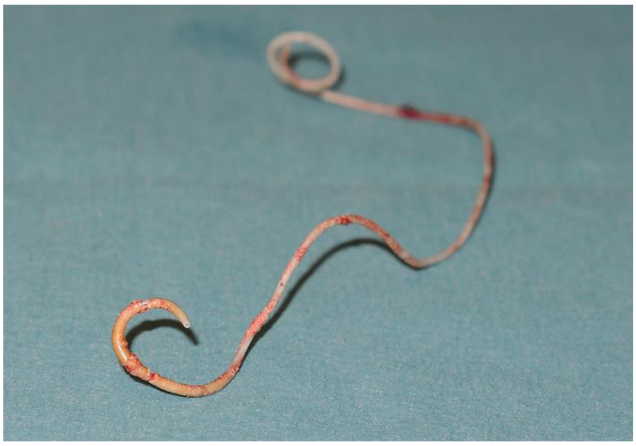
Legend: a double-pigtail ureteral *stent* was placed to bypass nephroliths and ureteroliths (black arrow).

Complications resulting from ureteral *stenting* were mostly minor and in lower rates than those reported with traditional ureteral surgery (Berent et al., 2014). The reported complications rate is approximately 9% to 17% in the postoperative period, 9% until 30 days after the surgery and 33% in the long-term period, with a postoperative mortality of approximately 8 to 18%

(Horowitz, Berent, Weisse, Langston & Bagley, 2013; Berent et al., 2014; Kulendra, Syme, Benigni & Halfacree, 2014; Culp et al., 2016; Wormser et al., 2016; Deroy et al., 2017).

The most frequently described complications were signs of dysuria (pollakiuria or stranguria) in 35% to 48% of cats and a ureteral *stent* exchange was needed in 27% to 44% of cats, which was more frequent in cats with ureteral stricture (Berent et al., 2014; Kulendra et al., 2014; Wormser et al., 2016; Deroy et al., 2017). Signs of dysuria reported in cats were typically temporary and resolved spontaneously or with medical management, normally consisting in steroid administration or α-adrenergic blockage (Lamb, Vowler, Johnston, Dunn & Wiseman, 2011; Berent et al., 2014). The exact cause of these signs remains unclear. Nevertheless, it is thought to be caused by the irritation of the distal pigtail of the *stent* in the trigone region and proximal urethra and by ureteral smooth muscle spasm (Lamb et al., 2011). The *stent*'s material, position of the *stent* and extra length that remains inside the urinary bladder may also contribute to the origin of dysuria (Berent et al., 2014; Deroy et al., 2017). A ureteral *stent* exchange was required due to a reobstuction of the ureter, and consequently *stent* occlusion, in 19% of cats, *stent* migration in approximately 6% of cats and because of *stent* irritation in 3% of cats (Berent et al., 2014). Fracture and encrustation (which also leads to a device occlusion) of the ureteral *stent* may also occurs (figure 9), demanding a *stent* exchange (Kulendra et al., 2014).

Figure 9. Retrieved double-pigtail ureteral *stent* with extensive mineralization (adapted from Deroy et al., 2017).



Legend: double-pigtail ureteral *stent* removed from a cat with an obstructive ureterolithiasis several months after placement because of encrustation.

Urine leakage was also a common complication of ureteral *stenting*, being described in approximately 15 to 23% of cats (Kulendra et al., 2014; Culp et al., 2016; Deroy et al., 2017). Similarly, cats who developed a uroabdomen postoperatively because of urine leakage were significantly less likely to survive (Culp et al., 2016).

Another common complication is chronic lower urinary infection, diagnosed in 11% of cats in a study conducted by Wormser et al. (2016). In fact, infection was significantly more common in cats with a ureteral *stent* than in cats that underwent a ureteral surgery. Contrary to Humans, ureteral *stent*s are usually left in place long-term in cats and it has been established that the incidence of *stent* related urinary tract infection is directly related to the duration of *stenting*. Once the device is colonized by bacteria, a biofilm formation may occurs, which makes the infection clearance more challenging (Klis, Korczak-Kozakiewicz, Denys, Sosnowski & Rozanski, 2009). Clinicians should carefully considered this when opting for ureteral *stenting*, and owners should be informed about the infection risk and possible need for a device replacement or removal (Wormser et al., 2016)

The median survival time of cats treated with ureteral *stenting* was between 419 and 498 days and the degree of residual renal function is vital since cats with CKD IRIS stage I and II lived longer than cats with CKD IRIS stage III and IV (Horowitz et al., 2013; Berent et al., 2014; Kulendra et al., 2014).

Contemplating the results of these recent studies, ureteral *stenting* may be considered as an effective treatment of feline ureterolithiasis with postoperative morbidity and mortality rates lower that those reported with traditional ureteral surgery (Berent et al., 2014). Nevertheless, the outcome of ureteral *stenting* are more successful for dogs than for cats (Berent, 2011).

2.5 Subcutaneous Ureteral Bypass (SUB)

Within the last few years, SUB devices had been introduced as a palliative treatment for the management of feline ureterolithiasis and, although reports of the use and outcome of cats with SUB devices are limited in the veterinary literature, it appears to improve the survival rate as well as the complications rate (Berent, Weisse, Bagley & Lamb, 2018). Given that, SUB devices are preferred for the management of ureterolithiasis in cats (Deroy et al., 2018; Milligan & Berent, 2019).

The SUB can be considered for the treatment of all causes of ureteral obstruction. An appropriate practical training with this device is essential before using it on an animal, in order to optimize the cat's outcome (Lulich et al., 2016; Berent & Weisse, 2018).

2.5.2 Surgical procedure

A SUB device (Norfolk Vet Products®) consists in a locking-loop pigtail nephrostomy catheter attached via a shunting port to a multi-fenestrated locking-loop cystostomy catheter, as showed in figure 10 (Berent & Weisse, 2018).

Figure 10. The SUB device put together outside of the patient (adapted from Berent & Weisse, 2018).

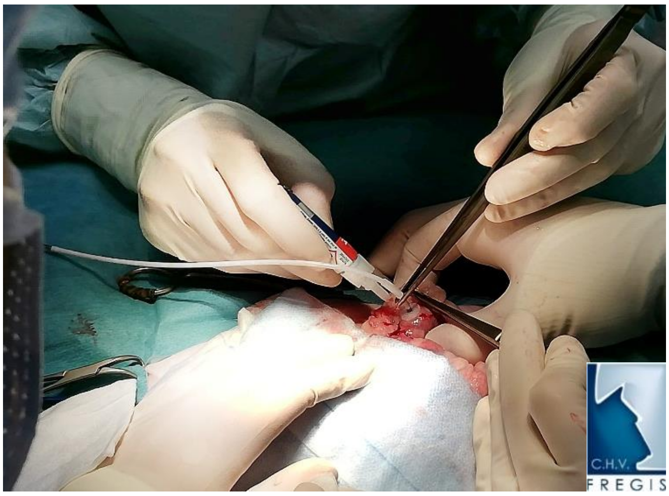
With the aid of fluoroscopy, the nephrostomy catheter is placed by use of the modified Seldinger technique. First of all, a ventral midline laparotomy is performed to expose the urinary bladder apex and the affected kidney; and the peri-renal fat is gently dissected off the caudal pole of the kidney, exposing a 1 to 2 cm region of the renal capsule. A 18 G over-the-needle catheter is used to puncture the renal pelvis at the caudal pole of the kidney (figure 11). A urine sample is then obtained for bacterial culture and an iohexol diluted with equal volume of sterile saline solution is injected into the renal pelvis to perform an antegrade pyelography. Under fluoroscopy guidance, a 0.035'' J-tip guidewire is advanced through the catheter and coiled inside the renal pelvis with the utmost attention to avoid perforation. Once 1 to 2 loops are made within the renal pelvis, the catheter is removed while the guide wire is carefully secured within the renal pelvis and then, the locking-loop pigtail nephrostomy catheter is advanced over the wire (figure 12). After it enters the renal pelvis, the guidewire is removed and the locking string is pulled, creating a pigtail inside the renal pelvis to prevent the catheter dislodgement.

Figure 11 and figure 12. Nephrostomy access into the kidney (adapted from Berent & Weisse, 2018 and original, kindly provided by the CHV-Frégis, respetively).

Legend: Left frame: 18G catheter (black arrow) puncturing the renal pelvis through the caudal pole of the kidney. Right frame: the nephrostomy catheter is advanced over the wire.

The black radiopaque marker of the nephrostomy catheter marks the last fenestration of the catheter, which should always be within the renal pelvis. Fluoroscopy should aid to ensure this, as well as the appropriate draining and filling of the renal pelvis and absence of leaking. Afterwards, the dacron cuff is gently advanced down the nephrostomy catheter and sterile glue is applied between the dacron puff and the renal capsule in order to keep the catheter secure in the renal pelvis and to prevent leakage or dislodgement (figure 13) (Berent & Weisse, 2018; Berent et al., 2018).

Figure 13. Application of sterile glue to secure the catheter (original, kindly provided by the CHV-Frégis).

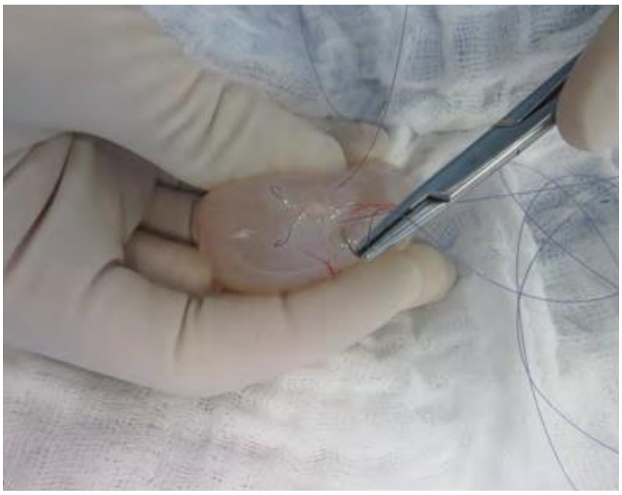


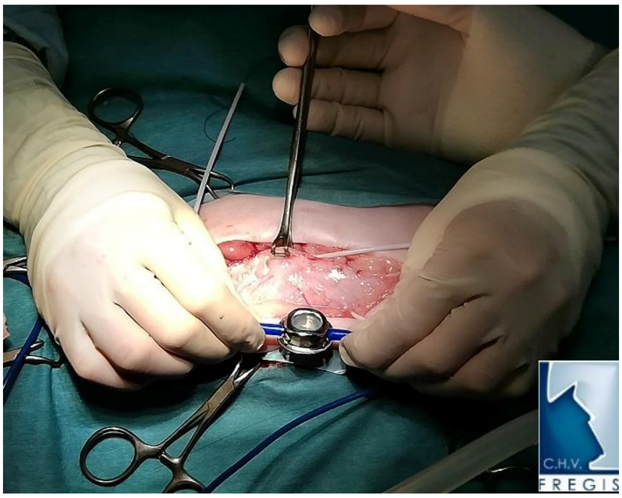
Guidelines for the SUB placement by Berent and Weisse (2018) recommend a different approach when the renal pelvis is < 8 mm, since the authors have found it easier and safer to place the nephrostomy catheter down the ureter instead of the renal pelvis. A 22 G IV catheter is inserted in the caudolateral aspect of the kidney angled toward the ureter. After confirmation of the direction of the catheter with fluoroscopy, a 0.018'' angle-tipped guide wire is advanced through the catheter and then this latter was removed over the wire. Afterwards, a 18 G catheter is advanced over the wire, which is removed and substituted with a 0.035'' angle-tipped guide wire and a nephrostomy catheter without the hollow cannula is advanced after the removal of the 18 G catheter. The nephrostomy catheter is modified previously: the locking string is cut to create a straight "ureterostomy" catheter. The rest of the procedure is performed as described above.

For the cystostomy catheter placement, a purse-string suture is placed (figure 14) at the apex of the urinary bladder and a stab incision is made in the center. In the case of a bilateral SUB placement, in order to both catheter sit as close as possible to the apex, each catheter should be placed just off the midline. The cystostomy catheter is then advanced into the urinary bladder until the radiopaque marker is within the lumen and a pigtail is formed. Afterwards, the purse-string suture is secured around the catheter and the dacron puff is suture and glued to the serosal surface of the urinary bladder. The utmost care should be taken to ensure that the catheter is not too far into the urinary bladder since this could be irritating and cause signs of dysuria in the cat. Following that, saline solution is infused through the catheter to ensure the absence of leakage (Berent & Weisse, 2018; Berent et al., 2018).

Finally, skin and subcutaneous tissues, immediately lateral to the ventral incision, on the ipsilateral side, are dissected down to the abdominal musculature. Both catheters are passed through the body wall and the shunting port is placed approximately hallway between the xiphoid and the pubis (figure 15). Once all parts positioned, a blue boot is placed over the catheters and the nephrostomy catheter is attached to the caudal aspect of the shunting port whereas the cystostomy catheter is connected to the cranial aspect, which maintain a gentle loop of the device and prevent kinks. Once the device is closed, it is leak tested to confirm the absence of leakage and afterwards, the shunting port is sutured to the ventral body wall. Topical bupivacaine is recommend in the subcutaneous pocket, around the shunting port. After the end of the surgery, fluoroscopy is performed to ensure that the catheters and the radiopaque markers are well situated in the renal pelvis and urinary bladder, with an appropriate filling of the renal pelvis and to confirm the absence of kinks and leakage (Berent & Weisse, 2018; Berent et al., 2018).

Figure 14 and figure 15. Placing the cystotomy catheter and shunting port (adapted from Berent & Weise, 2018 and original, kindly provided by the CHV-Frégis, respectively).





Legend: Left frame: a purse string suture is made at the apex of the bladder. Right frame: the shunting port is placed approximately hallway between the xiphoid and the pubis.

However, since access to fluoroscopy is sometimes limited, some surgeons are reporting effective and safe placement of the SUB device without fluoroscopy with no major difficulties or complications compared with the fluoroscopic guidance, demonstrating that a fluoroscopy is not essential in all cases (Deroy et al., 2017; Livet et al., 2017). The limitations of this technique are mostly related with the implantation of the nephrostomy catheter in cats with a minor pyelectasia and in cats with concurrent nephroliths, which reveals to be challenging/impossible without fluoroscopy (Livet et al., 2017).

2.5.3 Postoperative management

All animals should be carefully monitored during the postoperative period, with especial control of hydration status, urine output, anemia, serum concentrations of creatinine, BUN, phosphorus and potassium, among other biochemical parameters (Berent et al., 2018). An adequate postoperative analgesia and antimicrobial treatment is also important (Livet et al., 2017; Berent et al., 2018). There is evidence that cats that did not received antibiotics postoperatively had a significantly higher risk for the development of a positive urine culture after hospital discharge, (Berent et al., 2018; Kopecny, Palm, Drobatz, Balsa & Culp, 2019). Prior to hospital discharge, a flush of the SUB device is recommend, in order to ensure the absence of an occlusion of the device (Berent & Weisse, 2018; Berent et al., 2018).

2.5.4 Follow-up and flush of the SUB device

A regular follow-up of the animal is of major importance for an adequate control of the SUB device, the renal function and the clinical condition of the cat. Therefore, a serum biochemical profile, complete blood count, urinalysis, urine bacterial culture, abdominal ultrasonography with flushing of the SUB device and systolic blood pressure should be measured every 1, 3, 6, 9 and 12 months after the surgery and then every 3 to 6 months (Livet et al., 2017; Berent & Weisse, 2018; Berent et al., 2018). Flushing of the SUB device can be performed more regularly in animals with higher risk for device encrustation or for a urinary tract infection (Berent et al., 2018).

The SUB flushing is typically performed in a sterile manner using ultrasound guidance with minimal restraint of the animal. The fur over the shunting port is clipped and the skin is aseptically prepared. With a Huber needle in a perpendicular manner, a urine sample is obtained and submitted for urinalysis and bacterial culture. Afterwards, the device is flushed and the renal pelvis is monitored to confirm its distension and to avoid an overfilling of the renal pelvis. Then, the same volume of fluid is aspired and this procedure is repeated for the urinary bladder (Berent & Weisse, 2018; Berent et al., 2018). The SUB device may also be flushed under fluoroscopic guidance, in which the fluid is mixed with the contrast (Berent & Weisse, 2018).

It is recommended to infuse tetrasodium ethylenediaminetetraacetic acid (tetra-EDTA) for the flushing of the device, since this substance helps to prevent the formation of biofilm, mineralization and occlusion of the device (Berent & Weisse, 2018). This substance functions also as an anticoagulant and antimicrobial agent, therefore, protocols for flushing of SUB devices with mineralization and infection are available (Norfolk Vet Products, 2018).

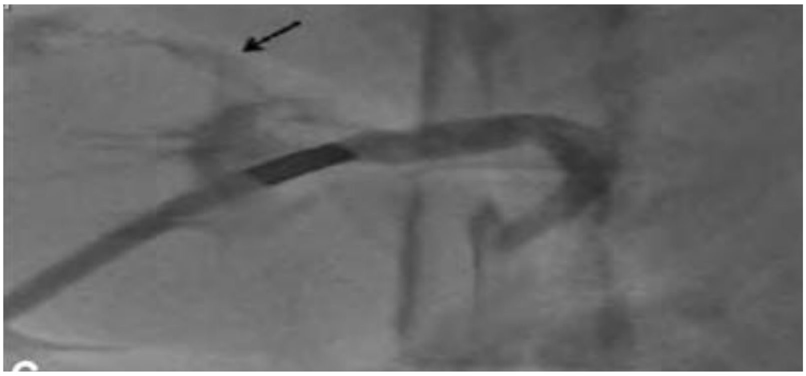
2.5.4 Complications

Since the introduction of the SUB device, both short-term and long-term complications have improved for cats with ureterolithiasis (Milligan & Berent, 2019). Many of the complications reported were technical and can be avoided with a previous proper training (Berent & Weisse, 2018).

Intraoperative complications were not common, reported in approximately 0% to 7% of cats, which included leakage of urine from the SUB device, occlusion of the device with blood clot, kinking of the catheters and iatrogenic renal hemorrhage (Horowitz et al., 2013; Deroy et al., 2017; Berent et al., 2018). Livet et al. (2017) reported an intraoperative complications rate of 15% in 13 cats. One of the two complications in this study was caused by a misplacement of the nephrostomy catheter, possibly secondary to an absence of fluoroscopic guidance.

Nevertheless, Deroy et al. (2017) also did not use fluoroscopy in the SUB surgeries of 23 cats and did not report any intraoperative complications.
Urine leakage from the SUB device or from the urinary tract resulted, in the majority of times, from technical errors during the surgery associated with the cut of the locking strings not close enough of the catheter (figure 16). Therefore, urine leakage was frequently founded at the junction of the shunting port and the catheters, where the locking strings were secured (Berent & Weisse, 2018; Berent et al., 2018). This complication was only described in the intraoperative and perioperative period, in approximately 0 to 3% of cats or 3.5% of SUB devices (Deroy et al., 2017; Luca et al., 2017; Berent et al., 2018).

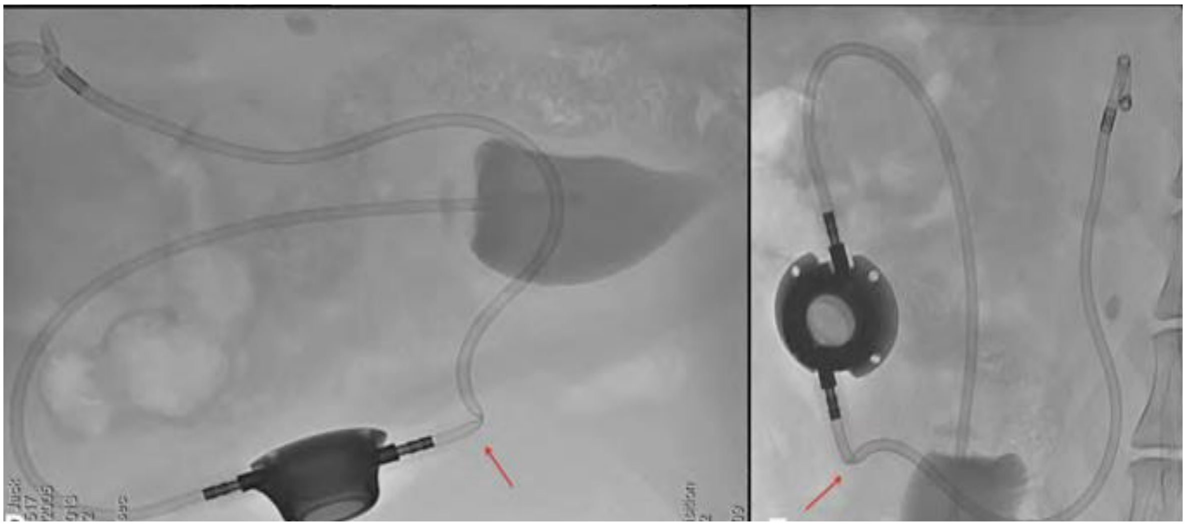
Figure 16. Fluoroscopic image showing leakage of the contrast from the kidney (adapted from Berent & Weisse, 2018).



Legend: Leakage of contrast (black arrow) seen at the cranial pole of the kidney. This was due to inadvertent guide wire puncture of the renal pelvis which was of no clinical consequence.

Kinking of the SUB device was also a complication described early after the surgery and, most frequently, resulted also from a technical error during the surgery (figures 17 and 18). To avoid this, it is important to connect the cystostomy catheter to the cranial aspect of the shunting port and the nephrostomy catheter to the caudal aspect, as well as place the shunting port hallway between the xiphoid and the pubis, in which a rule may useful for accomplish this latter (Berent & Weisse, 2018; Berent et al., 2018). Approximately 5% of devices presented this complication (Berent et al., 2018).

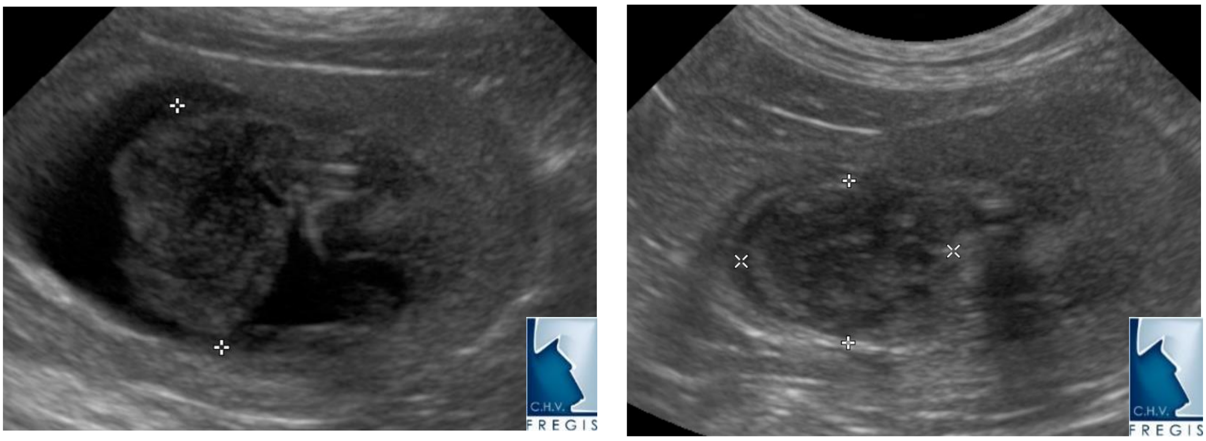
Figure 17 and figure 18. Fluoroscopic images of kinking of the SUB device (adapted from Berent & Weisse, 2018).



Legend: kinked SUB devices (red arrow).

Occlusion of the SUB device was reported in approximately 5 to 10% of cats or 8 to 24% of SUB devices (Deroy et al., 2017; Livet et al., 2017; Luca et al., 2017; Berent et al., 2018). Blood clot or mineralization were the main causes of occlusion of the SUB device, in which an obstruction caused by blood clots was usually identified within the first month after surgery while mineralization was almost always described in the long-term period. When a blood clot was present, flushing of the SUB device with tissue plasminogen activator resolved the occlusion in 36% of cases (figures 19 e 20) (Berent et al., 2018). Therefore, the use of this substance appears to be promising since it may avoid more invasive means of blood clot dissolution or extraction and prevent a surgery for device exchange (Hoii & Lemetayer, 2017). A case of a cat with perioperative occlusion of the SUB device secondary to a severe pyonephrosis was recently reported by Vedrine (2017). Repetitive flushing of the device successfully resolved the obstruction, therefore it may be considered an effective treatment for these cases.

Figure 19 and figure 20. Abdominal ultrasonographies showing the diminution of a blood clot in the renal pelvis (original, kindly provided by the CHV-Frégis).



Legend: Left frame: important hydronephrosis of the kidney with a blood clot obstructing the SUB device. Multiple flush with tissue plasminogen activator resolved the obstruction. Right frame: 24 hours after the device flush with tissue plasminogen activator, the renal pelvis and blood clot reduced their dimensions.

Mineralization of the SUB device was also a long-term complication identified in 4% of cats by Deroy et al. (2017) and in 24.5% of devices by Berent et al. (2017). Approximately half of the cases required a device exchange (figure 21). However, the other half did not need any further treatment since the affected ureters had become patent again. There is evidence that, once an ureterolithiasis is managed and the ureter is decompressed, a decrease in the luminal edema and hydrostatic pressure occur and, in some cases, the ureterolith can pass (Berent et al., 2018). Yet, the passage of ureteroliths leads to an increased risk for urethral obstruction with those ureteroliths, which was reported in one cat by Deroy et al. (2017) and another cat by Livet et al. (2017). With the use of tetra-EDTA solution for flushing SUB devices, the rate of mineralization has been declining, and a specific protocol is available as an attempt to minimize the mineralization incrusted in the device (Norfolk Vet Products, 2018). Flushing of the SUB with this solution is especially important in cats with a higher risk of encrustation of the device, such as in cats with hypercalcemia, since a postoperative ionized hypercalcemia was significantly associated with postoperative occlusion from mineralization or in cats with a previous history of device mineralization (Berent & Weisse, 2018; Berent et al., 2018).

Figure 21. Retrieved SUB devices from a cat with an obstruction due to mineralization (adapted from Deroy et al., 2017).

Legend: Asterisk: nephrostomy catheter. Dagger: cystotomy catheter.

Signs of dysuria were present in approximately 4% to 38% of cats but its presence did not seem to adversely affect the quality of life of cats, according to owners' opinion (Deroy et al., 2017; Livet et al., 2017; Luca et al., 2017; Berent et al., 2018). Compared to ureteral *stenting*, placement of a SUB device have lower rates of dysuria, which may be a result of the location of the device, since both devices are made of the same material. While the cystotomy catheter of the SUB device is placed at the apex of the urinary bladder, the ureteral *stent* may cause an irritation in the urothelium, given that the curl is positioned at the trigonal region and cranial to the proximal portion of the urethra (Berent et al., 2014; Deroy et al., 2017; Livet et al., 2017; Berent et al., 2018). Furthermore, when a ureteral *stent* was replaced by a SUB, in cats presenting refractory signs of dysuria, an immediate resolution of this sign was noted (Deroy et al., 2017; Berent el al.,2018). The occurrence of dysuria after the placement of a SUB device was significantly associated with a previous existence of signs of dysuria before the surgery (Berent et al.,2018).

A positive urine bacterial culture was documented in 24 to 31% of cats and the most common microorganism isolated consisted of *Enterococcus spp* (Livet et al., 2017; Berent et al., 2018; Kopecny et al., 2019). The importance of this bacteria in cats with urinary implants lies in both its mechanisms for antimicrobial resistance as well as its capacity to the formation of biofilms on the devices, making the infection clearance challenging (Kopecny et al., 2019). The most recent guidelines from the ISCAID indicate that, for the treatment of a sporadic bacterial cystitis, amoxicillin is a reasonable first choice antibiotic, likewise trimethoprim-sulfonamides.

When these are not available or appropriate, nitrofurantoin, fluoroquinolones and 3rd generation cephalosporins may be considered (even if it is controversial due to antibioresistance policy). The same guidelines suggest that treating a subclinical bacteriuria with antimicrobials is rarely indicated and discouraged. When it is uncertain if clinical signs are attributed to cystitis, antimicrobials may be used during a short course (3 to 5 days). These recommendations are also valid for multidrug resistant bacteria, since these organisms are not more likely to cause disease that their susceptible counterparts. Moreover, anecdotal information suggests that when the treatment is withheld, multidrug resistant organisms may, sometimes, be replaced with susceptible organisms. Currently, there is no evidence that adjunctive treatment, such as cranberry extracts or probiotics, are effective for the prevention of subclinical bacteriuria, but it is not contraindicated to use supplements that are known to be safe (Weese et al., 2019).

Although currently, there is no consensus regarding the classification of the resistance profile of bacteria in the veterinary medicine, the important increase of antimicrobial resistance in the recent years, suggests that further categorization is needed in order to communicate the true clinical impact of antimicrobial resistance (Magiorakos et al., 2012; Sweeney, Lubbers, Schwarz & Watts, 2018). As already stated, there is evidence that cats that did not receive antibiotics postoperatively had a significantly higher risk for the development of a positive urine culture after hospital discharge, (Berent et al., 2018; Kopecny et al., 2019). Moreover, cats that had a urinary tract infection before the surgery were more likely to develop another urinary tract infection after the SUB device placement (Berent et al., 2018). For these cats, with a higher risk for infection, flushing of the SUB with the tetra-EDTA solution is especially important to help the infection's clearance (Berent & Weisse, 2018; Berent et al., 2018; Norfolk Vet Products, 2018).

Anemia was identified in approximately 15 % of cats, and this may be because of an underlying CKD, excessive blood sampling during previous hospitalizations or due to inflammation (Shipov & Segev, 2013; Livet et al., 2017).

2.5.5 Outcome and Prognosis

Results of a recent study including 134 cats showed that for all cats the SUB device was successfully placed, there was an immediate renal decompression (Berent et al., 2018). The placement of the SUB device was associated with an overall survival time of 827 days and an overall mortality rate of 15% to 28% (Deroy et al., 2017; Livet et al., 2017; Berent et al., 2018). There is no record of mortality of cats during the surgery excepting for 2 cats who died during the anesthesia recovery period. The mortality rate associated with the placement of a SUB device was approximately between 5 and 15% in the perioperative period, 3% in the short-term period (between 7 and 30 days after the procedure) and 11% in the long-term period (>30 days after the procedure) (Horowitz et al., 2013; Deroy et al., Livet et al., 2017; Berent et al., 2018). Berent et al. (2018) reported that the serum creatinine concentration and IRIS stage 3 months after the device placement were the only postoperative factors significantly associated with the overall survival time in which cats with IRIS stage I and II had a significantly increased overall survival. Moreover, Horowitz et al. (2013) had the same results, with the addition of creatinine before discharge and IRIS stage at 6 months were also associated with the overall survival time. When it comes to preoperative factors, a previous history of CKD, a history of weight loss and the development of fluid overload prior to the surgery were the only preoperative factors significantly associated with the overall survival time (Berent et al., 2018).

Despite the existence of few investigations and research works regarding this subject, results from recent studies suggested that placement of the SUB device is a viable alternative in cats with ureteroliths and, overall, owners rated a high quality of life of theirs cats, following the placement of the device (Livet et al., 2017; Berent et al., 2018). This suggests an overall good prognosis, but the outcome is largely determined by the progression and severity of the underlying CKD after the decompression of the kidney. Cats with a more advanced CKD therefore have a more guarded prognosis (Horowitz et al., 2013; Deroy et al., 2017; Berent et al., 2018).

Results and outcome should, however, be interpreted and analyzed in a critical manner since the longest SUB device has been indwelling for 8 years in a cat, therefore, outcome beyond this point are unable to be ascertained (Berent & Weisse, 2018).

3. MATERIAL AND METHODS

3.1 Introduction and Objectives

The ureteral obstruction is becoming more frequent, especially in cats, with the most common cause being an intraluminal obstruction secondary to ureterolithiasis. They require immediate care, in order to prevent a decrease in renal function, regardless of whether the obstruction is partial or complete (Lulich et al., 2016). Renal decompression in cats can be realized traditionally but given the potential complications and mortality associated with these procedures, alternatives have been investigated for animals over the past years. Veterinary Interventional Medicine research has been looking for a less invasive technique that leads to an immediate renal decompression and stabilization of the azotemia while simultaneously prevent postoperative complications (Berent, 2011; Milligan & Berent, 2019).

Recently, sucbuctaneous ureteral bypass (SUB) placement has been considered for the treatment of the main causes of ureteral obstruction. Although SUB devices appear to improve the survival rate and outcome in cats with ureteral obstruction, reports about their complications and outcome are limited in the veterinary literature (Lulich et al., 2016; Berent, et al., 2018).

This study aims to evaluate the outcome of cats with SUB devices used for the treatment of ureteral obstruction, to describe short-term and long-term complications associated with this surgical procedure as well as to identify factors that may have an influence in the occurrence of these complications.

3.2 Experimental design

For this study, case records of cats that underwent a SUB placement in the *Centre Hospitalier Vétérinaire* Fregis, France, between February 2014 and January 2019 were retrospectively identified by use of a computerized medical database search with the coding term "subcutaneous ureteral bypass".

The study variables regarding the population's characterization and preoperative information that were recorded included: age, sex, reproductive status, race, clinical signs, previous history of chronic kidney disease (CKD) or other concomitant diseases, suspected ureteral obstruction's cause, localization of uroliths, if a medical management was attempted, measurements of the transverse plane of the renal pelvis and ureteral dilatation. Data concerning preoperative laboratorial findings were also collected: serum concentrations of BUN and creatinine at admission, presence of serum potassium concentration disorders, anemia and urine specific gravity (USG) at admission.

In the postoperative period, the information assembled consisted on: placement of unilateral or bilateral SUB device, measurement of the renal pelvis after surgery, serum concentrations of BUN and creatinine (24 hours after the surgery, at the hospital discharge and 7 days after the surgery), presence of serum potassium concentration disorders, presence of anemia, duration of hospitalization and occurrence of complications. Specific complications that were assessed consisted on: eventual SUB device occlusion, urine leakage from the device or urinary tract, mineralization of the device, bacteriuria, anemia, clinical signs of dysuria and deaths of a suspected renal cause. Then, complications were classified in major complications and minor complications. Major complications included device occlusion, urine leakage and mineralization of the device whereas minor complications included a positive urine culture, anemia and signs of dysuria.

Complications associated with placement of the SUB device were assessed in the intraoperative period (from the time of anesthetic induction until full recovery from the anesthesia), in the perioperative period (from full recovery to 7 days after surgery) and in the postoperative period divided into a short term (1, 3, and 6 months) and a long term (1, 2, 3 and 4 years after surgery) whenever possible. In the postoperative period, the serum concentration of urea and creatinine, as well as the measurement of the renal pelvis, were registered at these times.

Whenever a bacterial culture was positive, an antimicrobial susceptibility testing (AST) was performed. The urine was seeded in chromogenic agar (Biomérieux) with a 10 microlitre inoculation loop. The method utilized in the AST was the disk diffusion test, with concentrations of antibiotics according with the Veterinary Antibiotic Committee of the French Society of Microbiology (CASFM). The break points were also automated according the Veterinary CASFM (*Comité de l'antibiogramme de la Société Française de Microbiologie Vétérinaire*, 2018; *Comité de l'antibiogramme de la Société Française de Microbiologie*, 2019). Afterwards, if the bacteria had a resistance profile, it was classified, based in the standard definitions of an international expert proposal by Magiorakos et al. (2012) for human medicine. However, considering that many drugs are not authorized in the French country, fewer antibiotics are tested in the AST comparing in other countries. Bacteria with a low level of antimicrobial resistance was considered when non-susceptibility to at least one agent in three or more antimicrobial categories was presented; a medium level of antimicrobial resistance was considered for non-susceptibility of the bacteria to at least one agent in all but two or fewer antimicrobial categories and a high level of antimicrobial resistance was given for bacteria with a non-susceptibility to all agents in all antimicrobial categories.

Dysuria is typically manifested as pollakiuria and/or stranguria (Berent et al., 2014; DiBartola, S. P. & Westropp, J. L., 2014), therefore, these clinical signs are included in the variable signs of dysuria.

From referred cats, the information provided by the primary veterinarian, such as history and blood and urine analysis, were included in the present study.

The duration of hospitalization was defined as the time between the day of the surgery until the day of the hospital discharge. When owners requested a hospital transfer to their primary veterinary hospital, the remaining days in their facilities were also considered, if the information was available.

Criteria for safe discharge from the hospital included good clinical condition and appetite as well as an important decrease in the serum creatinine concentration. Recommendations for stimulation of the water consummation and implementation of a renal diet were suggest to owners, at the hospital discharge.

3.4 Routine hospital procedures concerning cats undergoing SUB placement

Routinely, before surgery, cats undergo abdominal ultrasonography performed by board-certified diagnostic imaging specialists or residents under their supervision. The ureteral obstruction was diagnosed based on the identification of a hydronephrosis with an associated hydroureter and/or the identification of ureteroliths.

The medical management consists essentially in an aggressive intravenous fluid therapy combined with analgesia. Frequently, an osmotic diuretic, typically furosemide, can also be administered, according to the clinician's decision.

In the preoperative period, the drugs routinely administered to cats are: morphine (0.2 mg/kg, slow IV) and midazolam (0.2 mg/kg, IV). General anesthesia is induced with propofol and maintained with volatile isoflurane. Surgery is performed by board-certified surgeons and third and second-year surgical residents, under their supervision. An open surgical approach without the aid of fluoroscopy is commonly performed in all cats, as well as a complete abdominal exploration, and any abnormalities identified were noted. Affected ureters are located and the location of the obstruction is noted, when identified.

The SUB device (Norfolk Vet Products®) includes a 6.5F locking-loop catheter and a multifenestrated 7F catheter, placed as a nephrostomy and cystostomy tube, respectively. A urine sample is routinely obtained intraoperatively for a bacterial culture and an antimicrobial susceptibility testing.

Postoperative radiographic study is performed in order to ensure that the SUB device is appropriately placed correctly in the kidney and bladder and there is no urine leakage or catheter kinking by contrast medium injection. A Huber needle (Norfolk Vet Products®) is used to inject, slowly through the shunting port, 3 mL of diluted (1:1) iohexol, followed by 3 mL of sterile saline (0.95% NaCl) solution to flush the contrast medium from the catheter.

For the postoperative pain control, all cats usually receive analgesia with buprenorphine, which is typically continued postoperatively. A combination of fentanyl, lidocaine and ketamine can also elected when severe signs of discomfort and pain are demonstrated by the cat. An antimicrobial therapy is instituted with a general duration of 4 to 8 weeks and multiple urine cultures are performed during and after the treatment.

Concerning postoperative controls, routine physical exams are performed 2 to 3 times a day. Serum creatinine and urea concentrations are monitored 24 to 48 hours post surgery and every 24 to 48 hours during hospitalization until stabilization of these parameters. If the parameters are not improving, a recheck ultrasound is routinely performed. One month after the surgery, a flush of the SUB device is recommend, as well as urine culture, urine protein-to-creatinine ratio, measurement of the phosphorus, ionized calcium, creatinine and urea concentration. Three months after the surgery, these latter parameters are monitored and a flush of the device is performed. It is suggested to owners to repeat the flush procedure, every 3 to 4 months. The blood pressure measurement is also routinely performed at the time of the control, when the clinician considered necessary.

3.6 Statistical analysis

Analysis was performed in order to determine whether preoperative and postoperative factors were associated with the occurrence of major complications and duration of the hospitalization. For qualitative variables, frequency analysis was performed with the $\chi 2$ or Fisher exact test, when appropriate. The quantitative variables were analyzed with the Wilcoxon signed-rank test. Numerical data were summarized as median and range.

The risk over time of major complications and the survival curve were determined with the Kaplan-Meier curve function. When the complication or death had not yet occurred, time to last follow-up was used to censor records.

In order to assess if a correlation was present between the serum creatinine concentration and the days passed in hospitalization, a Spearman's rank correlation test was performed, as well for the urea serum concentration.

Data obtained in the current study were stored in a Microsoft Excel 2016® datasheet and all statistical analysis were performed using The R Project for Statistical Computing version 3.6.0. Values of $p < 0.05$ were considered significant.

4. RESULTS

4.1 Characterization of the population

129 cats were included in this study. From them, 52% (67/129) were females and 48% (62/129) were males. 83% (107/129) were castrated cats whereas 17% (22/129) were sexually intact cats. Median age at the time of SUB device placement was 7.7 years (range 2 to 17 years).

There were 62% (80/129) domestic shorthairs, 12% (16/129) Birman, 5% (6/129) British Shorthair, 4% (5/129) Norwegian Forest Cat, 3% (4/129) Maine Coon and 14% (18/129) of other breeds. Other breeds included Chartreux (3), Persian (3), Bengal (2), Abyssinian (1), Angora (1), Balinese (1), Korat (1), Oriental Shorthair (1), Persian Chinchilla (1), Ragdoll (1), Russian Blue (1), Siamese (1) and Somali (1).

4.2 History and clinical findings at hospital admission

At hospital admission, the most common clinical signs included anorexia or dysorexia (61% [79/129] cats), lethargy (48% [62/129]), vomiting (40% [51/129]), weight loss (25% [32/129]), polyuria and/or polydipsia (16% [20/129]), signs of dysuria (9% [12/129]), oliguria or anuria (5% [7/129]), hematuria (3% [4/129]) and abdominal pain (3% [4/129]).

Laboratory testing performed at the initial evaluation revealed an anemia in 8% (10) of cats, with a median value of hematocrit of 19.6 % (range 14% to 24%; reference interval 25 to 45%), in these cats. The urine specific gravity was measure in 55 cats demonstrating a median value of 1,020 (range 1,005 to 1,050; reference interval > 1,035).

Median serum urea concentration was 227.47 mg/dL (range 34 to 569 mg/dL; reference interval 30 to 60 mg/dL) while median serum creatinine concentration was 8.57 mg/dL (range 1.5 to 27.2 mg/dL; reference interval 0.6 to 1.6 mg/dL).

Regarding electrolyte disorders, 19% (25; reference interval 3.5 to 4.8 mmol/L) of cats had a hyperkalemia while 4% (5) had a hypokalemia.

Before hospital admission, 13% (18) of cats were already being followed for a history of CKD. Other concomitant diseases were present in 12% (15) of admitted cats and included hypertrophic cardiomyopathy (5) and myxomatous mitral valve degeneration (2) as the most frequent concomitant diseases registered.

From these 129 cats, 5% (7/129) had previous surgeries of the urinary tract due to former ureteral obstructions. Ureteral *stents* were placed in 5 cats, in which 1 of them also had a cystotomy and ureterotomy performed and one had a cystotomy realized. For the other 2 cats, one had a nephrectomy and one an ureterotomy performed before their SUB placement.

4.3 Diagnostic imaging findings

Information about preoperative abdominal was available for 97% (125/129) of cats. Ureterolithiasis was the most common cause of ureteral obstruction and, therefore, ureteroliths were identified in 98% (122/125) of cats, in which 3 cats had an ureteral *stent* that obstructed. Other causes of ureteral were ureteral strictures, which were identified in 2% (2/122) cats and 1 cat (1/122) had recurrent cystitis caused by an ureteral *stent*.

The ureteral obstruction was found in the proximal portion of the ureter (proximal third of the ureter) in 49% (63) of ureters, in the mid portion (mid third of the ureter) in 24% (31), in the distal portion (distal third of the ureter) in 36% (46) and at the ureterovesicular junction in 9% (12) of ureters.

Hydroureter was found in 57% (77/135) of ureters, with a median ureteral diameter of 3.3 mm (range, 1 to 12 mm; reference interval < 0.4 mm). Hydronephrosis was also detected in 89% (150/168) of ureters, with a median renal pelvic diameter of 11 mm (range, 1.7 to 50 mm; reference interval < 1.6 mm), determined in the transverse plane.

Concomitant nephroliths were visualized in 32% (41) of cats, cystic calculi were present in 9% (11) of cats and 2% (3) of them also had a urethral lithiasis.

4.4 Ureteral obstruction management

There are records of a medical treatment attempted for 61% (79) of cats, before the SUB device placement. 65% (84) of cats underwent a unilateral SUB device placement and 35% (45) underwent a bilateral SUB device placement, for a total of 174 obstructed ureters. In the 84 cats in which a SUB device was placed unilaterally, 56% (47) had an obstruction in the right ureter and 44% (37) in the left ureter.

Concomitantly to the SUB device placement, other interventions were performed at the same surgical time in 6% (8/129) cats: a cystotomy in 3 cats for cystic calculi removal, nephrectomy of the contralateral kidney in 2 cats, urethrotomy in 2 cats and, in one cat, a ureteral *stent* in the contralateral ureter.

In one cat with a renal pelvic diameter of 3 mm, the implantation of the nephrostomy catheter in this minor pyelectasia showed to be challenging so, since fluoroscopy was not available, ultrasonography was used during the surgery in order to assist the nephrostomy placement into the renal pelvis.

4.5 Postoperative data

Median urea and serum creatinine concentrations 24 hours after SUB device placement were 166.2 mg/dL (range 23 to 434 mg/dL) and 4.6 mg/dL (range 0.5 to 17.8 mg/dL), respectively.

Median hospitalization time was 5 days (range 1 to 14 days) and approximately 12% (16) of cats died prior to hospital discharge.

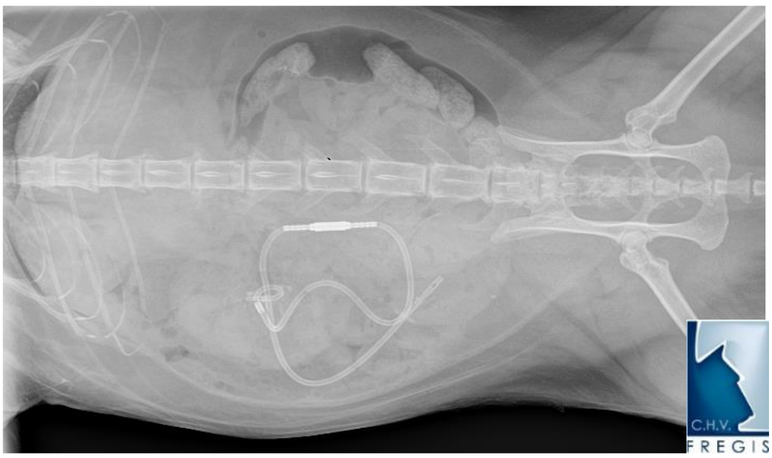
Median serum creatinine concentration recorded before hospital discharge was 2.5 mg/dL (range 0.9 to 13.2 mg/dL) and median serum urea concentration was 95.3 mg/dL (range 20 to 355 mg/dL).

4.6 Complications

4.6.1 Intraoperative complications

Complications occurred during the surgery in 3% (4/129) of cats. Two cats suffered from iatrogenic renal hematomas during the nephrostomy catheter's implantation. One of these cats had a degradation of its clinical condition the days subsequent the surgery as well as a worsening azotemia and aggravation of the renal lesions, which leaded to a consented decision of euthanasia, 2 weeks after the surgery. In 1 cat, the implantation of the nephrostomy catheter resulted in an important hemorrhage and sub capsular kidney urine leakage so, a reimplantation of this catheter had to be done. The last cat also had a urine leakage but from the nephrostomy catheter. Since this leakage could not be solved, another nephrostomy catheter was placed and connected to the cystotomy catheter with a male-male adaptor, because of the prolonged surgery's time (figure 22). Despite all of that, no deaths were described during the surgery time.

Figure 22. Dorsoventral view radiograph of a cat with a male-male adaptor (original, kindly provided by the CHV-Frégis).



4.6.2 Perioperative complications

Information on complications occurring since full recovery from the anesthesia to 7 days after surgery was available for 116 of 129 cats. Documented complications included occlusion of the SUB device system in 10% (12/116) of cats, leakage from the SUB device in 3% (4/116) of cats, a positive urine culture in 9% (10/116) of cats, signs of dysuria in 10% (12/116) of cats and anemia in 14% (16/116) of cats. In the 4 cases of leakage, a second surgery was needed for the replacement or reconditioning of the SUB device. In the 16 cats with anemia, the median value of the hematocrit was 17.3 % (range 10% to 24%).

During this period, a mortality rate of approximately 14% (16/116) was identified.

4.6.3 Short-term and long-term complications

Complications were characterized at 1, 3 and 6 months and 1, 2, 3 and 4 years after the SUB device placement, when information was available.

4.6.3.1 Complications 1 month after SUB device placement

Information on complications that occurred 1 month after the placement of the SUB device was available for 61 (47%) cats. The most common complications detected were: occlusion of the SUB device system in 2% (1/61) of cats, leakage from the SUB device in 2% (1/61) of cats, an positive urine culture in 18% (11/61) of cats, signs of dysuria in 18% (11/61) of cats and an anemia in 7% (4/61, median value of hematocrit of 18%) of cats and mineralization of the device in 2% (1/61) of cats. One cat had a second surgery performed for the reconditioning of the SUB device following a leakage of urine from the device.

During this period, the mortality rate was approximately of 3% (2/61).

4.6.3.2 Complications 3 months after SUB device placement

Three months after the surgery, information was available for 52 from 129 (40%) cats. From these, 8% of cats (4/52) had evidence of occlusion of the SUB device, 13% (7/52) had a positive urine culture and 8% (4/52) of cats presented signs of dysuria. Anemia was not observe in any of the cats.

One additional cat was euthanized, which conferred a mortality rate, between 1 month and 3 months post surgery, of 2%.

4.6.3.3 Complications 6 months after SUB device placement

The most common complications identified 6 months after surgery, in the 49 (38%) animals where data were available, were a positive urine culture in 20% (10/49) of cats and evidence of dysuria's signs in 16% (8/49) of cats. More severe complications were present in a fewer number of animals, with an occlusion of the SUB device in 10% (5/49) of cats, mineralization of the device in 2% (1/49) of cats and leakage of urine from the device in 2% (1/49) of cats. Anemia was only observed in 1 cat which had a hematocrit of 19%.

A second surgery was needed for 4 cats (8%) for replacement or reconditioning of the SUB device due to urine leakage from the device in 1 (2%) cat and because of an obstruction due to mineralization of the device in 3 (6%) cats (figure 23).

There are record of 1 from the total of 49 cats was euthanized, which confer a mortality rate of 2% between 3 and 6 months after SUB device placement.

Figure 23. Dorsoventral view radiograph showing the absence contrast in the renal pelvis (original, kindly provided by the CHV-Frégis).

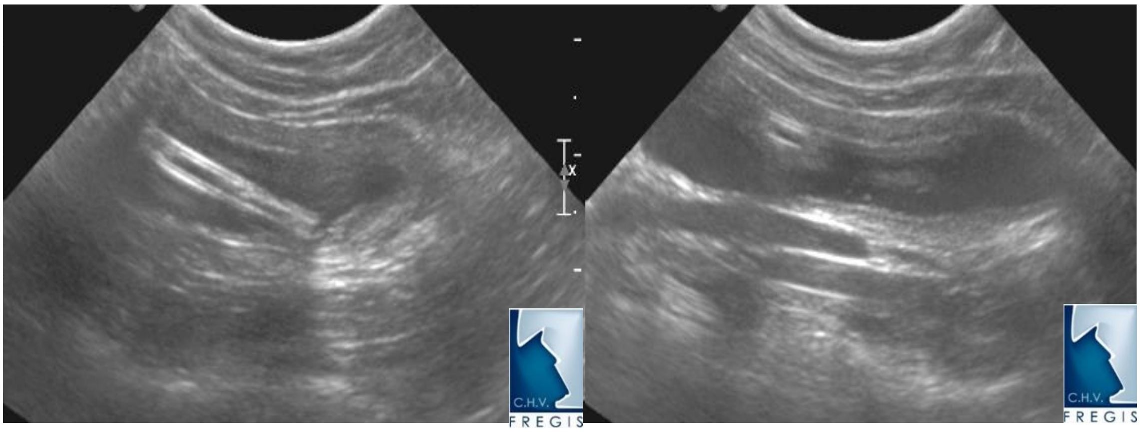
Legend: The absence of contrast revealed an occlusion in the nephrostomy catheter. The cat had a second surgery for the replacement of this catheter.

4.6.3.3 Complications 1 year after SUB device placement

Fifty one (40%) of 129 cats had available information on complications occurring 1 year after the surgery. Documented complications included occlusion of the SUB device system in 20% (10/51) of cats, mineralization of the device in 6% (3/51) of cats, positive urine culture in 22% (11/51) of cats, signs of dysuria in 22% (11/51) of cats and 2% (1/51) of cats had an anemia with a hematocrit of 16%.

A second surgery had to be performed for replacement or reconditioning of the device in 10% (5/51) cats and for removal in 2% (1/51) cat. Four (8%) cats needed to replace the SUB due to the complete obstructions of the device while one cat (2%) had the distal extremity of the cystotomy catheter cut, due to a distal displacement of the catheter inside the urinary bladder. This resulted in chronic signs of dysuria and thickening of the urinary bladder's wall (figure 24 and 25). One (2%) cat had a nephrectomy performed because of advanced and severe kidney lesions associated with a chronic bacteriuria, therefore the SUB device was removed.

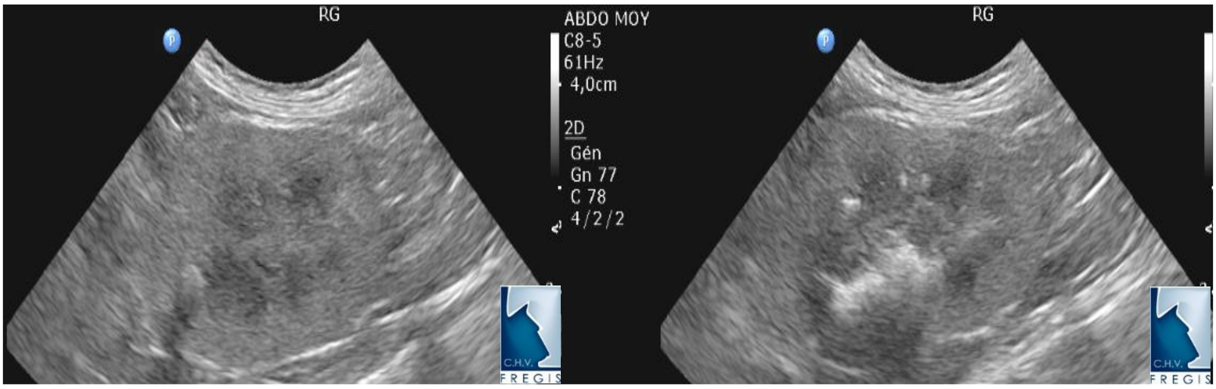
Figure 24 and figure 25. Abdominal ultrasonographies showing a distal displacement of the cystotomy catheter (original, kindly provided by the CHV-Frégis).



Legend: The cystotomy catheter is 2 cm inside the urinary bladder. The urinary bladder's wall is thickening and irregular with 4 mm of thickness.

One year and 6 months after the surgery, an abdominal ultrasound exam of one (2%) cat showed that its nephrostomy catheter was adhered to an intestinal loop, although flushing of the SUB device was not affected. Since a device occlusion was not presented, the owner decided to not remove the SUB device (figures 26 and 27).

Figure 26 and figure 27. Adherence of the nephrostomy catheter to an intestinal loop (original, kindly provided by CHV-Frégis).



Between 6 months and 1 year after the surgery, the mortality rate was 4% (2/51). In one (2%) of the cats a euthanasia was decided, since it had a severe renal insufficiency associated with a severe hyperkalemia, resulting from the obstruction of the device. This obstruction leaded also to the dilatation of the ipsilateral ureter with formation of an ampoule of 20 mm in the proximal portion of the ureter.

4.6.3.4 Complications 2 years after SUB device placement

For the 34 cats (36%) for which follow-up information was available, 26% (9/34) had an obstruction of the SUB device, 15% (5/34) had evidence of mineralization of the device, 29% (10/34) had an positive urine culture, 24% (8/34) demonstrated signs of dysuria and an anemia was presented in 6% (2/34, median value of hematocrit of 16.5%) of cats.

A second surgery was performed in 2 (6%) cats, one for replacement of the SUB device and the other for its removal. In the latter case, the distal portion of the cystotomy catheter was completely adherent to a jejunal loop and even penetrated inside the loop, so the device had to be removed and a partial cystectomy and enterectomy were performed. In the meanwhile, the ureters of this cat showed signs of re-permeability, therefore, a second SUB device was not placed.

One cat presented a cutaneous fistula at the level of the subcutaneous shunting port, with a purulent discharge, in which the bacteria *Enterobacter cloacae* was identified (the bacteria had already been identified in the urinary tract).

Between 1 year and 2 years after the surgery, a mortality rate of approximately 3% (1) was identified, in which the cat was euthanized.

4.6.3.5 Complications 3 years after SUB device placement

Information about complications occurring 3 years after surgery was only available in 16 cats (12%). The most common complications detected were: occlusion of the SUB device system in 31% (5/16) of cats, mineralization of the device in 13% (2/16) of cats, a positive urine culture in 25% (4/16) of cats, signs of dysuria in 13% (2/16) of cats and the presence of an anemia in 1 cat (7%, value of the hematocrit 16.5%).

In one cat, a second surgery was performed in order to remove the SUB device. A caudal displacement of the nephrostomy catheter resulted in a subscapular kidney abscess with engagement of the ipsilateral ureter, pancreas and duodenum in the abscess. Additionally, there was also an absence of permeability of the device whereas the ureters evidenced a recuperation of the permeability, hence the need to the device's removal.

Nearly 3 years after the surgery, in one cat, the abdominal ultrasound exam revealed an incarceration of the nephrostomy catheter in one intestinal loop. The ultrasound exam and the flush did not show signs of obstruction neither the animal had clinical signs of it, therefore the owners declined the recommendation from the clinicians to remove the device.

There are records of one death, which conferred a mortality rate of 6%, between 2 and 3 years after the SUB placement.

4.6.3.6 Complications 4 years after SUB device placement

Only 4 cats had available information on complications, 4 years after the surgery. An occlusion of the SUB was found in one cat, but a flushing of the device restored the device's permeability. Another cat had a positive urine culture along with signs of dysuria.

In the table 1, the short and long-term complications are summarized.

Table 1. Summary of short and long-term complications of the SUB device placement.

Time after surgery	Obstruction	Leakage	Minerali zation	Dysuria	Bacteriuria	Anemia	Mortality rate
7 days (n=116)	10%	3%	0%	10%	9%	14%	14%
1 month (n=61)	2%	2%	2%	18%	18%	7%	3%
3 months (n=52)	8%	0%	0%	8%	13%	0%	2%
6 months (n=49)	10%	2%	2%	16%	20%	2%	2%
1 year (n=51)	20%	0%	6%	22%	22%	2%	4%
2 years (n=34)	26%	15%	0%	24%	29%	6%	3%
3 years (n=16)	31%	0%	13%	13%	25%	7%	6%
4 years (n=4)	25%	0%	0%	25%	25%	0%	0%
Overall (n=129)	32%	5%	8%	25%	19%	19%	19%

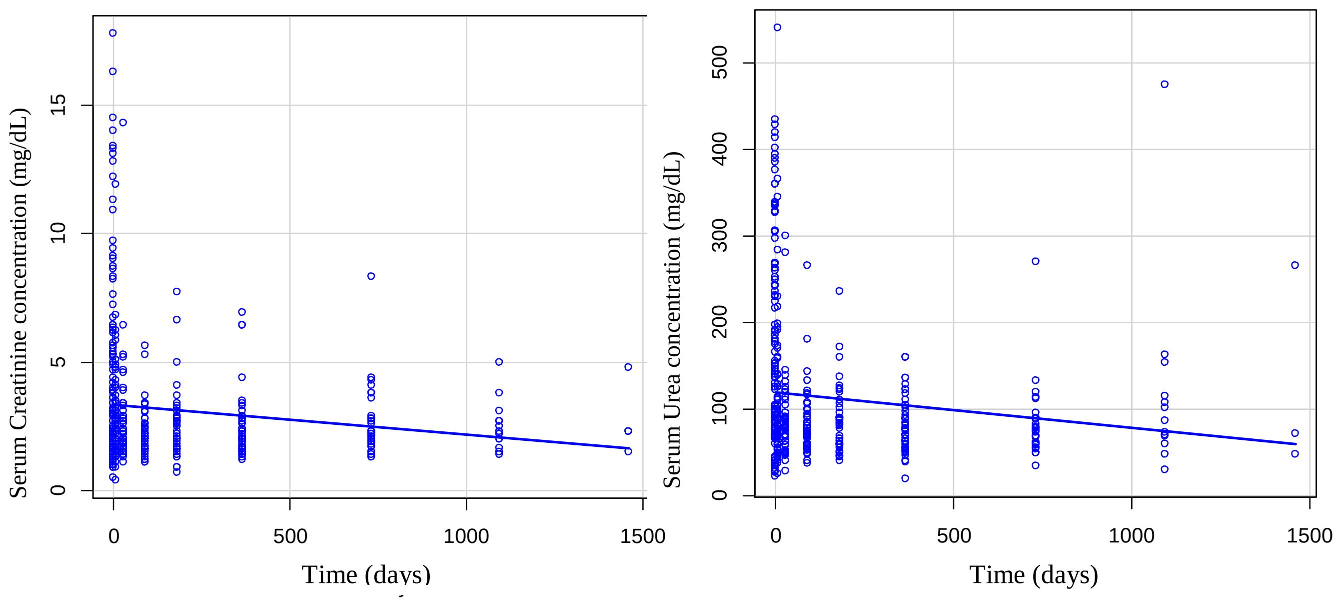
4.7 Follow-up information

Median serum creatinine concentrations at 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years and 4 years after surgery were 3 mg/ dL, 2.7 mg/dL, 2.4 mg/dL, 2.5 mg/dL, 2.4 mg/dL, 2.6 mg/dL, 2.5 mg/dL and 2.7 mg/dL (figure X), respectively.

Median urea creatinine concentrations at 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years and 4 years after surgery were 110 mg/ dL, 83.7 mg/dL, 88.8 mg/dL, 86 mg/dL, 86 mg/dL, 79.8 mg/dL, 87.9 mg/dL and 128 mg/dL (graph 1), respectively.

Median renal pelvis diameter measured ultrasonographically in the transverse plane at 1 week, 1 month, 3 months, 6 months, 1 year, 2 years and 3 years after surgery were 5.6mm, 3.8mm, 5.4mm, 5.3mm, 4.1mm and 5mm, respectively.

Graph 1.Variation of the serum creatinine and urea concentrations through time.



Overall, complication rate, any time after the surgery, of cats that underwent a SUB device placement was: 5% (6) of cats had urine leakage, 8% (10) had mineralization of the SUB device, 32% (41) had an occlusion of the device, 29% (38) presented signs of dysuria, in 25% (32) a positive urine culture was obtained and 19% (25) of cats were anemic. Therefore, 38% (49) of cats had major complications while 56% (72) of cats had minor complications.

A second or more surgical interventions were needed for the replacement or reconditioning of the SUB device in 16 cats (12%).

From the 129 cats, 24 (19%) died of a suspected renal or ureteral cause of death, any time after the surgery.

A positive urine bacterial culture result was documented for 32 of 129 (25%) cats at some time after SUB device placement. Organisms isolated at any time after surgery consisted of *Escherichia coli* (13), *Klebsiella pneumoniae* (6), *Enterobacter cloacae* (6), *Staphylococcus spp* (5), *Pseudomonas aeruginosa* (4), *Enterococcus spp* (3) and other (6). The most common antibiotics employed were beta-lactams (16), fluoroquinolones (10), tetracyclines (6) and a combination of trimethoprim-sulfamethoxazole (6). Exceptionally, 8 cats (6%) did not receive antimicrobial treatment, either because the bacteria had a resistance profile or because a subclinical bacteriuria was present. Neither of these cats presented any different clinical sign due to the cease of the antibiotic treatment.

Results from the AST revealed that, any time after surgery, 10 cats had a positive urine culture with an antimicrobial resistance identified. From these, 2 cats had a low level of resistant bacteria, 2 cats had a medium level of resistant bacteria, 2 cats had a high level resistant bacteria and 4 cats had an initial medium level resistant bacteria identified and, in later urine culture, the same bacteria was identified with a low level resistance. Therefore, this happened also to another cat, in which an initial urine culture isolated a low level resistant bacteria and, multiple urine cultures latter, the same bacteria no longer presented a resistance profile. These 5 cats had an antibiotic treatment initially however, it did not solved the bacteriuria and, for this reason, clinicians decided to stop the antibiotic treatment. Several urine cultures after the interruption of the treatment, the bacteria revealed itself susceptible to more antibiotics and resistant to less antibiotics than before.

The site of the SUB device obstruction was recorded for 19 cats in the nephrostomy catheter and for 12 cats in the cystotomy. Information about the cause of the obstruction was recorded for 10 cats: for 6 cats a blood clot caused the occlusion of the device, in 3 cats a mineralization of the device was the cause and for 1 cat, the cause was a urinary tract infection. A flush of the device was performed in order to solve the obstruction and information was available for 29 cats: in 19 (66%) cats, the flush resolved the obstruction and in 10 (34%) cats, the obstruction did not resolved itself with the flush.

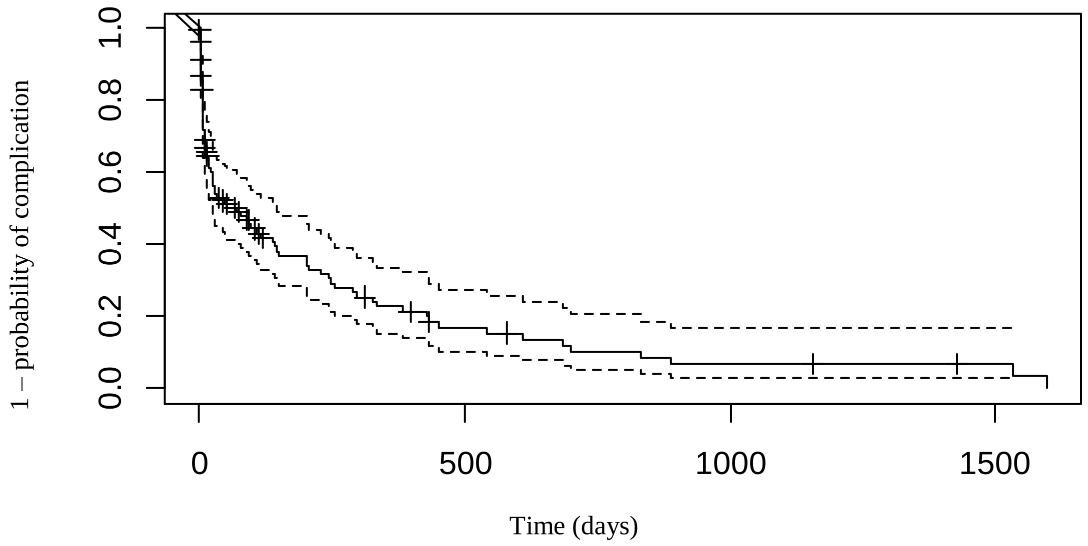
In 5 cats with occlusion of the device, a restoration of the permeability of the ureters was evidenced because of an absence of a pyelectasia, worsening of the azotemia and anuria or oliguria. From these, two cat had to remove its device, one because of a medium resistant bacteria associated with the device was presented and the other cat because the nephrostomy catheter was causing a subscapular kidney abscess. The other 3 cats kept their SUB devices.

Information about the location of the mineralization of the SUB device was not always available but it was recorded that 9 cystotomy catheters and 5 nephrostomy catheters presented mineralization, any time after the surgery.

4.8 Risk factor analysis

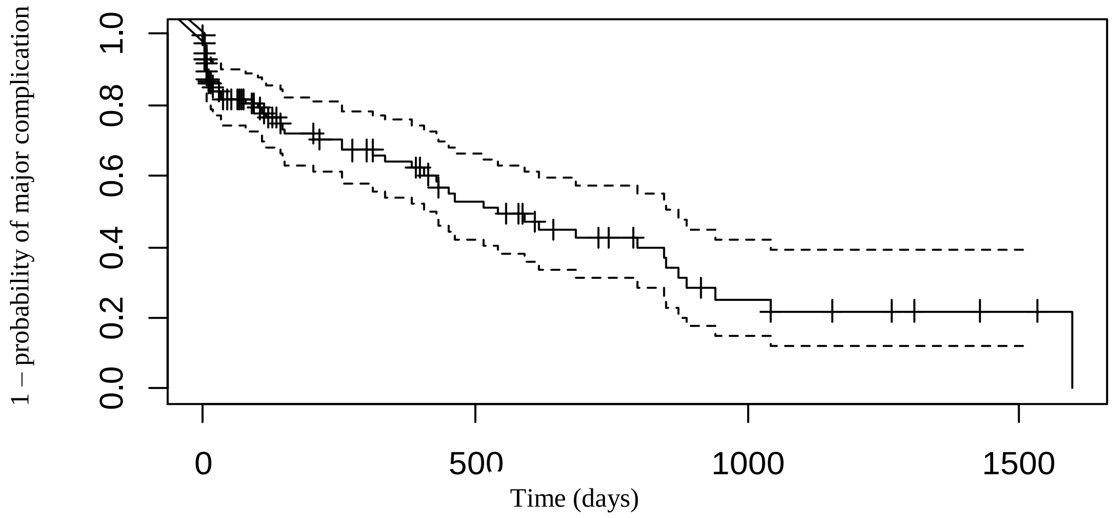
The function of the probability of occurrence of a complication was obtained based in a Kaplan-Meier curve, which reveals that 50% of cats had a first overall complication on a mean of 72 days after the surgery, as presented in the graph 2.

Graph 2. Kaplan-Meier curve for cats with overall complications after the placement of the SUB device.



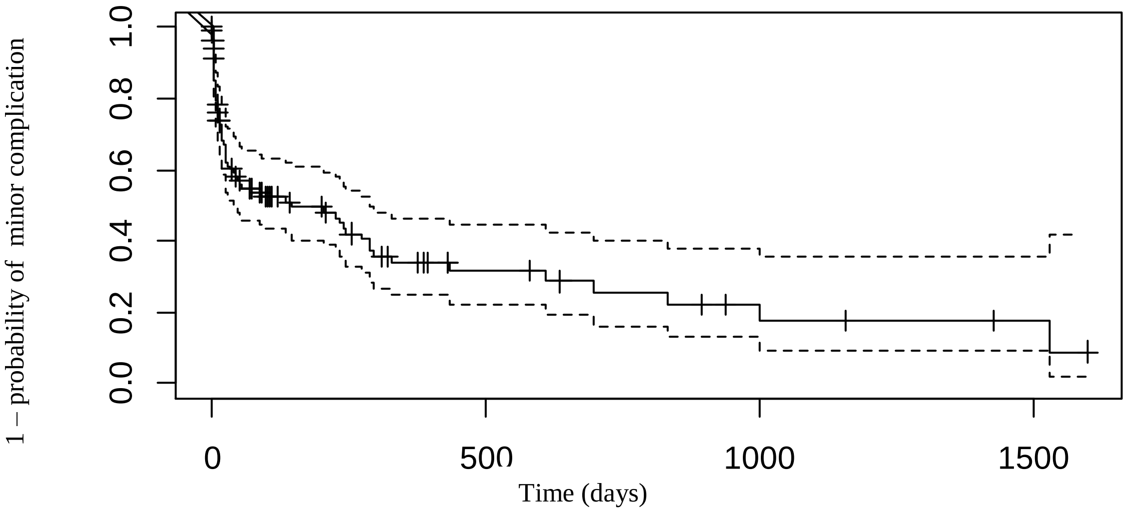
However, when taking into account only major complications, 50% of cats presented a major complication on a mean of 541 days after the surgery, as presented in the graph 3.

Graph 3. Kaplan-Meier curve for cats with major complications after the placement of the SUB device.



In the other hand, considering just minor complications, these were identified earlier in time, as demonstrated in the graph 4, in a mean of 148 days after the placement of the SUB device.

Graph 4. Kaplan-Meier curve for cats with minor complications after the placement of the SUB device.



The age of the cats was not significantly associated with complications (w = 1836.5, p = 0.8), regardless of being a major (w = 1749, p = 0.42) or minor complication (w = 2208, p = 0.3). Sex also did not had an influence in the occurrence of complications ($\chi 2$ (1) = 0.47, p = 0.5), major ($\chi 2$ (1) = 0.32, p = 0.57) or minor ($\chi 2$ (1) = 0.05, p = 0.83), neither the reproductive status was associated with overall complications ($\chi 2$ (1) = 2.5, p = 0.11), major ($\chi 2$ (1) = 3.09, p = 0.07) or minor complications ($\chi 2$ (1) = 0.12, p = 0.73).

The occurrence of a complication was significantly associated with anorexia or dysorexia ($\chi 2$ (1) = 6.72, p = 0.009), in which a complication was identified in a mean of 24 days after the placement of the SUB *versus* 203 days for cats without anorexia or dysorexia at hospital admission. However, none of the following clinical signs at hospital admission had a significantly association with overall complications: signs of dysuria ($\chi 2$ (1) = 0.5, p = 0.48), weight loss ($\chi 2$ (1) = 1.11, p = 0.29), polyuria or polydipsia ($\chi 2$ (1) = 0.62, p = 0.43), vomiting ($\chi 2$ (1) = 0.38, p = 0.54), lethargy ($\chi 2$ (1) = 2.48, p = 0.12), oliguria or anuria ($\chi 2$ (1) = 1.13, p = 0.29) and abdominal pain ($\chi 2$ (1) = 0.1, p = 0.74). Hematuria was only presented in 4 cats preoperatively, therefore no statistics analysis were able to be performed.

Regarding major complications, lethargy at hospital admission ($\chi2$ (1) = 3.92, p = 0.048) and oliguria or anuria ($\chi2$ (1) = 7.16, p = 0.007) were significantly associated with the occurrence of a major complication. Cats presented with lethargy had a major complication identified in a mean of 430 days after the placement of the SUB *versus* 797 days for cats without lethargy and oliguric or anuric cats at the hospital admission presented a major complication a mean of 11 days after the surgery *versus* 591 days for cats without oliguria or anuria. Other clinical signs were did not had an association: signs of dysuria ($\chi2$ (1) = 0.12, p = 0.72), weight loss ($\chi2$ (1) = 0.6, p = 0.44), polyuria or polydipsia ($\chi2$ (1) = 0.04, p = 0.84), vomiting ($\chi2$ (1) = 0.95, p = 0.33), anorexia or dysorexia ($\chi2$ (1) = 3.46, p = 0.06) and abdominal pain ($\chi2$ (1) = 0.3, p = 0.59).

Concerning minor complications, a significant association was found with anorexia or dysorexia ($\chi2$ (1) = 6.32, p = 0.01). A minor complication was identified 42 days *versus* 296 days for cats who were not anorexic or dysorexic at the hospital admission. Other clinical signs did not had an association: signs of dysuria ($\chi2$ (1) = 0.18, p = 0.67), weight loss ($\chi2$ (1) = 1.66, p = 0.2), polyuria or polydipsia ($\chi2$ (1) = 0.17, p = 0.68), vomiting ($\chi2$ (1) = 0.04, p = 0.85), lethargy ($\chi2$ (1) = 0.02, p = 0.89), oliguria or anuria ($\chi2$ (1) = 0,73 p = 0.4) and abdominal pain ($\chi2$ (1) = 0.62, p = 0.43).

The serum concentration urea at hospital admission did not influence the development of complications (w = 1268.5, p = 0.88), major (w = 1495.5, p = 0.84) or minor (w = 1395, p = 0.58) neither the serum concentration creatinine at the hospital admission influenced the occurrence of complications (w = 1365, p = 0.91), major (w = 1451, p = 0.74) or minor (w = 1526, p = 0.92). Regarding serum potassium concentration disorders identified before the surgery, hyperkalemia was not significantly associated with complications ($\chi2$ (1) = 0.004, p = 0.95), (major ($\chi2$ (1) = 0.05, p = 0.82) or minor ($\chi2$ (1) = 0.12, p = 0.72). Since hypokalemia was only identified in 5 cats preoperatively, no static analysis were able to be performed.

Preoperative anemia was not significantly associated with complications ($\chi2$ (1) = 0.02, p = 0.88), major ($\chi2$ (1) = 0.32, p = 0.57) or minor ($\chi2$ (1) = 1.06, p = 0.3). Preoperative urine specific gravity was not significantly associated with complications (w = 282.5, p = 0.75), major (w = 445.5, p = 0.23) or minor (w = 335.5, p = 0.58).

Interestingly, a previous history of CKD was found to be significantly associated with minor complications ($\chi2$ (1) = 0.29, p = 0.03). However, overall complications ($\chi2$ (1) = 0.38, p = 0.54) or major complications ($\chi2$ (1) = 0.19, p = 0.66) did not had an association with a history of CKD. A history of other concomitants diseases was not significantly associated with the development of complications ($\chi2$ (1) = 0.43, p = 0.51), major ($\chi2$ (1) = 0.92, p = 0.37) or minor ($\chi2$ (1) = 0.04, p = 0.84).

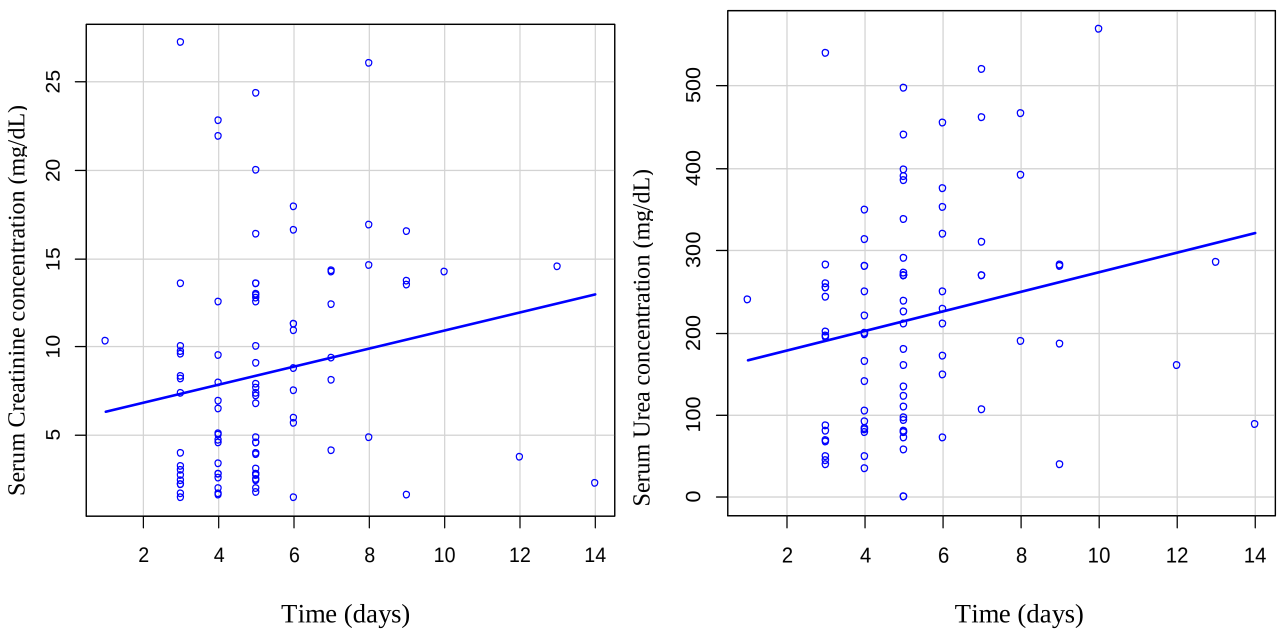
The placement of a bilateral SUB device was not significantly associated with complications ($\chi2$ (1) = 1.1, p = 0.3), regardless of being major ($\chi2$ (1) = 3.49, p = 0.06) or minor complications ($\chi2$ (1) = 0.5, p = 0.48).

The duration of the hospitalization was not significantly associated with the occurrence of complications (w = 1204, p = 0.42), regardless of being major (w = 1236.5, p = 0.68) or minor complications (w = 1205, p = 0.6).

A weak positive correlation between the serum creatinine concentration at hospital admission and the hospitalization time (rho = 0.29, p = 0.005) likewise a weak positive correlation between the serum urea concentration at hospital admission and hospitalization time (rho = 0.28, p = 0.007) were identified. As demonstrated in the graph 5, the duration of the hospitalization tended to increase with higher concentrations of serum creatinine and urea at hospital admission.

The hospitalization time was significantly associated with oliguria or anuria at hospital admission (w = 189, p = 0.04) as well as with anorexia or dysorexia (w = 915.5, p = 0.04). Other clinical signs such as abdominal pain (w = 161, p = 0.15), hematuria (w = 270, p = 0.21), weight loss (w = 965, p = 0.52), vomiting (w = 1282, p = 0.94), lethargy (w = 1065, p = 0.08), polyuria and polydipsia (w = 701, p = 0.79) and signs of dysuria (w = 549, p=0.13) were not significantly associated with the days spent in the hospital.

Graph 5. Correlation between the serum creatinine and urea concentration at admission and hospitalization time.



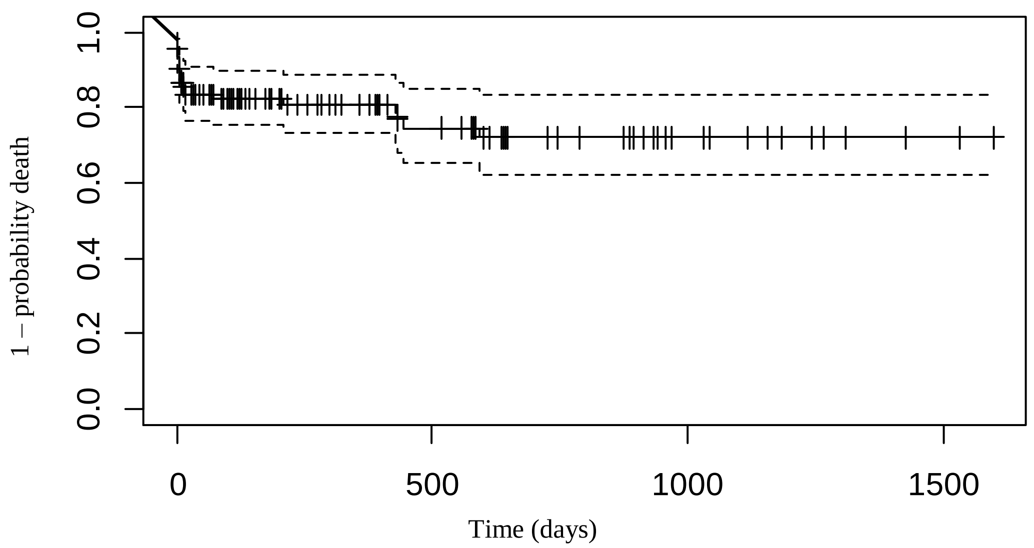
The serum concentration urea at hospital discharge did not influence the development of complications (w = 944, p = 0.83), major (w = 1089, p = 0.89) or minor (w = 1042.5, p = 0.88) neither the serum concentration creatinine at the hospital admission influenced the occurrence of complications (w = 1004, p = 0.56), major (w = 1192.5, p = 0.62) or minor (w = 1112.5, p = 0.8).

The need for a second or more surgical interventions after the device placement was significantly associated with the occurrence of complications ($\chi2$ (1) = 8.82, p = 0.003), major complications ($\chi2$ (1) = 19.01, p < 0.001, or = 15.26) and minor ($\chi2$ (1) = 4.8, p = 0.04, or = 3.24). Therefore, cats submitted to further surgical interventions were 5 times more likely to develop major complications than minor ones.

The development of signs of dysuria any time after the surgery was not significantly associated with preoperative signs of dysuria (x_2 (1) = 1.04, p = 0.3). Neither episodes of anemia in the postoperative period was significantly associated with preoperative anemia (x_2 (1) = 1.26, p = 0.26).

Interestingly, overall complications (x_2 (1) = 0.008, p = 0.93), major complications (x_2 (1) = 0.003, p = 0.96) or minor complications (x_2 (1) = 0.03, p = 0.86) were not significantly associated with death of cats with a suspected renal or ureteral cause. A survival curve demonstrated that 25% of cats died of suspected renal or ureteral cause a mean of 444 days after the SUB device placement (Graph 6).

Graph 6. Kaplan-Meier survival curve of survival days of cats after the placement of the SUB device.



The death of cats with a suspected renal or ureteral cause was not significantly associated with the placement of a bilateral SUB device (x_2 (1) = 0.42, p = 0.51), history of CKD (x_2 (1) = 0.18, p = 0.67), other concomitant diseases (x_2 (1) = 2.43, p = 0.12) or second or more surgeries after the SUB placement (x_2 (1) = 0.02, p = 0.98). Moreover, any of the clinical signs registered at hospital admission were significantly associated with the mortality.

Complications founded in these cats were not associated with the IRIS stage 1 month (w = 132, p = 0.68), 3 months (w = 207.5, p = 0.42), 6 months (w = 54.5, p = 0.27), 1 year (w = 103.5, p = 0.47), 2 years (w = 28, p = 0.05) and 3 years (w = 11, p = 0.91) after the surgery. Neither major or minor complications were also founded to be associated with the IRIS stage after the renal decompression.

5. DISCUSSION

In this study, SUB devices were successfully placed in all cats, without fluoroscopic guidance, and only few cats experienced major postoperative complications. To the author's knowledge, there is only two studies (Deroy et al., 2017; Livet et al., 2017) that described this procedure without fluoroscopy in the placement of a SUB device in 23 and 13 cats. Therefore, this study reinforces the success and safety of the implantation of the SUB device without the need of fluoroscopy. The surgeons are normally exposed to radiation when fluoroscopy is used and, since this equipment is not always accessible, this approach without fluoroscopy allows more surgeons to use SUB devices, with less individual and team risk. Despite that, there are some limitations associated that should be considered namely the complications that can come from the implant of the nephrostomy catheter in a minor pyelectasia or in the presence of nephroliths (Livet et al., 2017). In this present study, the implantation of the nephrostomy catheter had to be performed with ultrasound guidance (because fluoroscopy was not available) in one cat with a renal pelvic diameter of 3 mm, because the placement of the catheter presented difficulties during the surgery.

The overall mortality rate was 19%, which is in agreement with previous published results (Deroy et al., 2017; Livet et al., 2017; Berent et al., 2018).

Although the major cause of ureteral obstruction in the present study was ureterolithiasis, ureteral strictures and a recurrent cystitis by a ureteral *stent* also leaded to a SUB placement. Concurrently to the ureteral obstruction, nephroliths were also identified. Their presence could be a risk factor for reobstruction of the ureter since they have the potential to eventually pass into the ureter and obstruct it.

After the diagnosis of ureterolithiasis, 61% of the cats in this study tried a medical treatment, in order to promote the spontaneously passage of the calculi, without reaching success in all of them. It is known that reported effective results of this therapy are very low and a risk of irreversible renal damage during medical management should not be ignored, stressing the individual need of judgement about the length of this option. Above all, the renal function should be preserved at any cost, since the probability of urolith's recurrence in cats is high and, therefore, when attempting for the medical therapy, this should not be applied for more than 72h (Kyles et al., 2005b; Lulich et al., 2016).

Regarding intraoperative complications, these were rare and consisted on iatrogenic lesions in the kidney during the implantation, hemorrhage and urine leakage from the catheter. Despite that, no intraoperative deaths were identified. These complications had no major consequence, except for one of the cats who suffered from iatrogenic lesions with progressive degradation of its clinical condition leading to a consented decision of euthanasia, 2 weeks later. Its clinical aggravation may have been a consequence of the combination of: intraoperative iatrogenic lesions, an important and prolonged preoperative degradation of its clinical condition and the presence of signs of CKD at the time of the diagnosis. In fact, more than the previous CKD, a prolonged anesthesia time could have influenced the renal which can get worse with possible intraoperative complications such as hypothermia and hypotension (Kulendra et al., 2014; Livet et al., 2017; Luca et al., 2017). In this case, the iatrogenic lesions during the surgery could have been related to the fact that the implantation of the nephrostomy catheter was performed without fluoroscopic guidance into a renal pelvis presenting a minor pyelectasia of only 3.8 mm. In the two previous studies in which fluoroscopy was not used, only one major intraoperative complication was reported, consisting in kinking of the nephrostomy catheter (Deroy et al., 2017; Livet et al., 2017). This complication was not identified in the cats of this study.

Concerning postoperative complications, a classification into major or minor was performed. This is mainly due to the fact that several complications such as dysuria or bacteriuria were typically temporary and resolved spontaneously or medically. Anemia was considered a minor complication. It may be a result of an underlying CKD, excessive blood sample or inflammation (Shipov & Segev, 2013; Livet et al., 2017). Nonetheless, anemia was not severe in any of those cases and was, therefore, not considered a major complication. Therefore, major complications associated with the SUB placement in the cats of this study were device occlusion (n=41, 32%), mineralization of the device (n=10, 8%) and urine leakage from the device or urinary tract (n=6, 5%). These results are somewhat different from those previously reported. In this study, the occurrence of device occlusion is much higher compared with the reported (Deroy et al., 2017; Livet et al., 2017; Luca et al., 2017) but, in the other hand, kinking of the device was not founded in this study whereas in other studies this was identified in 5% of cases (Berent et al., 2018). The rate of urine leakage is approximately similar to the described in previous studies (Deroy et al., 2017; Luca et al., 2017) but mineralization of the SUB device was slightly higher in this study, compared to Deroy et al. (2017). Despite not very pronounced in this present study, urine leakage and kinking of a catheter typically occurred earlier after the surgery whereas mineralization of the device was almost always described in the long-term period (Berent et al., 2018).

Minor complications reported for cats in the present study were signs of dysuria in 29% (38) cats, a positive urine culture in 25% (32) of cats and an anemia in 19% (25) of cats. These values were consistent with the complication rate of previous studies (Deroy et al., 2017; Livet et al., 2017; Berent et al., 2018; Kopecny et al., 2019). Comparatively to ureteral *stenting* and traditional ureteral surgery, there are fewer complications associated with the placement of SUB devices, when this is appropriately managed and monitored (Kyles et al., 2005b; Berent et al., 2014; Kulendra et al., 2014; Culp et al., 2016; Wormser et al., 2016; Deroy et al., 2017).

Current recommendations suggest that, flushing of the SUB device should be performed every 3 to 4 months, in order to prevent a device obstruction (Berent & Weisse, 2018). With the advent of this recommendation, occlusions have been minimized (Berent, 2014). The causes of the obstruction in cats of the present study were blood clots, mineralization and possible plug due to a urinary tract infection. Occlusion of the device secondary to a urinary infection was only been described before in one cat, by Vedrine (2017), in which the ureteral patency was restored with repetitive flushing of the device. In the cat of the present study, flushing of the device did not resolved the occlusion and the SUB device was removed. In previous studies, tissue plasminogen activator was reported to solved 36% of the occlusions due to a blood clot, resulting in a promising alternative to other invasive means of blood clot dissolution or extraction (Hoii & Lemetayer, 2017; Berent et al., 2018). Recently, infusion of tetra-EDTA solution for flushing of SUB devices has been employed to both prevent and treat urinary tract infections related with biofilm, as well as, the mineralization and occlusion of the SUB device (Berent & Weisse, 2018). As a matter of fact, Berent et al. (2018) observed a considerable decline in the mineralization rate since the used of this material routinely. However, since this is a recent material, flushing of the devices in the present study was performed with NaCl 0.9%. This may explain the higher rates of mineralization and occlusion founded. Despite the large number of occlusions, more than a half of them were resolved with flushing, demonstrating, once again, that the mechanical effect of the flush prevent and treat SUB obstructions.

Several cats with occlusion of the device had the permeability of the native ureter restored. There is evidence of, once an ureterolithiasis is managed and the ureter is decompressed, a decreased in the luminal edema and hydrostatic pressure occurs and, in some cases, the passage of the ureterolith takes place (Berent et al., 2018). However, this may increase the risk for a urethral obstruction (Deroy et al., 2017; Livet et al., 2017).

Some of the cats of this study presented complications associated with adherence or penetration of a catheter of the SUB device into an intestinal loop, in which half of the devices became obstructed and, consequently, had to be removed whereas, in the other half, the flushing of the device was not affected. To the author’s knowledge, these complications had not previously been reported in the literature and this is the first study that identify them in cats treated with a SUB device. Therefore, this study informs and alerts for unexpected complications that can cause occlusion of the device and can also lead to clinical digestives signs, which was the case for the two cats with the device occlusion, that manifested dysorexia and vomits.

Compared with the rates reported for ureteral *stenting,* this present study, together with other studies, demonstrated that cats with a SUB device developed lower rates of dysuria, which is likely a result of the location of the device. While the cystotomy catheter of the SUB is placed at the apex of the urinary bladder, the ureteral *stent* is historically positioned at the trigonal region and cranial to the portion of the urethra, inducing irritation of the urothelium (Berent et al., 2014; Deroy et al., 2017; Livet et al., 2017; Berent et al., 2018). Furthermore, when a ureteral *stent* was replaced by a SUB in cats presenting refractory signs of dysuria, an immediate resolution of the dysuria was noted (Deroy et al., 2017; Berent el al.,2018). Despite Berent et al. (2018) founded that the occurrence of dysuria after the placement of a SUB device was significantly associated with a previous existence of signs of dysuria before the surgery, this was not evidenced in the present study. Regardless of all of this, owners do not considered dysuria adversely affected the quality of life of their cats (Berent et al., 2018).

Subclinical bacteriuria was reported in several cats in previous studies (Kopecny et al., 2019) and, according to the most recent guidelines from the ISCAID, the treatment of subclinical bacteriuria with antimicrobials, regardless of the resistance profile, is rarely indicated and discouraged. Moreover, anecdotal information suggests that, when the treatment is withheld, multidrug resistant organisms may, sometimes, be replaced with susceptible organisms (Weese et al., 2019). As a matter of fact, this was seen in some cats of this study, in which multiple urine cultures after the suspension of the treatment revealed an increase of susceptibility of the bacteria to antibiotics for which a resistance was recognized before. Therefore, this demonstrate that susceptible organisms may substitute multidrug resistant bacteria when not placed under an antimicrobial environment, at which treatment with routine antimicrobials may be more practical, if it becomes indicated (Weese et al., 2019). Although these results seem promising, further investigations are required to evaluate the response of multidrug resistance bacteria under different conditions.

Typically, minor complications tended to occurred much earlier (148 days after the surgery) than major complications (541 days after surgery). However, minor complication were normally easily managed and, for dysuria, its presence not seem to adversely affect the quality of life of cats, according to the owners opinion (Livet et al., 2017; Berent et al., 2018).

The only preoperative factor significantly associated with the occurrence of overall complications was the presence of anorexia or dysorexia before at hospital admission. These same clinical signs were also significantly associated with the occurrence of minor complications while major complications were significantly associated with lethargy and oliguria or anuria at the hospital admission. Despite most of these being no specific clinical signs, it may, in a way, help the clinician to anticipate certain complications.

Cats that had a known history of CKD before the ureteral obstruction episode were significantly associated only with the occurrence of minor complications. Cats with an advanced CKD may develop a uremic syndrome and anemia may be part of it (Shipov & Segev, 2013), so this may explain in part the association with minor complications.

The need for a second or more surgical interventions after the device placement was significantly associated with the occurrence of complications and these cats were 5 times more likely to develop major complications than minor ones. This may be because minor complications usually do not need surgery for their resolution unlike some major complications such as urine leakage and unresolved device obstructions. Nevertheless, some cats with a chronic bacteriuria, which was probably associated with the SUB device biofilm, needed a device removal in order to clear that bacteriuria. Moreover, a second surgery was also needed for a cat with chronic dysuria, for reconditioning of the cystotomy catheter. Despite that, surgeries are more likely to be performed for the management of major complications.

Interestingly, the mortality rate was not significantly associated neither with complications neither with other preoperative and postoperative parameters tested. This suggests that, predicting the patient outcome, prior and after the renal decompression, is difficult.

The main limitation of the present study was its retrospective nature, which resulted in follow-up parameters not perfectly homogeneous. A random selection of patients also did not occurred. Since this study included cats whom had SUB device placement until January 2019, in some cats, the follow-up period was too short to clearly establish long-term complications and outcome and, in particular, to compare. Some analysis and exams results were facilitated from the primary veterinary, therefore, different laboratories were involved, which may have affected result's consistency. Since many drugs are not allowed in France, the antimicrobial susceptibly testing may also have been performed with lesser drugs than the usual in other countries, which may have affected the classification of bacteria. Despite that, the cohorts of cats in the present study represent the second largest regarding the placement of SUB devices for the treatment of feline ureteral obstruction in the veterinary literature. Furthermore, the placement of the SUB device was performed only by board-certified surgeons and surgical residents with their supervision, in order to improve the cat's outcome.

Several limitations are, however, recognised in this study. Indeed, it would had been interesting the implementation of questionnaire for the owners, for them to provide information about clinical signs and the quality of life of their cats. Moreover, the recurrent record of the concentrations of serum phosphorus and ionized calcium have been of major interest, because the medical records of cats presented in this study rarely had this information available and those are parameters that can be dramatically affected by a ureteral obstruction and a renal disease. Also important would have been the study of crystalluria at the time of hospital admission. Also the medical treatment should have been better detailed in order to assess the potential relationship between the maximal delay of medical management until the SUB placement. Due to the retrospective nature of this study, this parameter could not be assessed.

Concerning future perspectives, an interesting study for the future would be to investigate the effects of not treating a subclinical bacteriuria in cats that have a positive bacterial urine culture, (as recommend in the recent guidelines from ISCAID [Weese et al. (2019]), and to compare those effects to subclinical bacteriuria treated with antimicrobials. Another interesting investigation can eventually be the comparison between complications associated with SUB devices flushed with NaCl 0.9% *versus* those flushed with the tetra-EDTA solution.

6. CONCLUSION

In the present study, SUB devices were introduced as palliative treatment for ureteral obstruction in cats, regardless of the cause and location of the obstruction. The surgical procedure was performed without fluoroscopic guidance, resulting in an effective and safe SUB placement, without revelant difficulties, demonstrating that fluoroscopy is not essential in all cases.

Major complications described consisted mainly in device occlusion (n=41, 32%), mineralization of the device (n=10, 8%) and urine leakage from the device or urinary tract (n=6, 5%). Likewise, minor complications were also founded: signs of dysuria in 29% (38) cats, a bacteriuria in 25% (32) of cats and an anemia in 19% (25) of cats. In contrast with previous studies (Berent et al., 2018), kinking of the device was not identified in the present study.

Minor complications were observed a mean of 148 days after the surgery and were significantly associated with anorexia or dysorexia at the hospital admission and a history of CKD. In the other hand, major complications were seen a mean of 541 days after the surgery and were associated with lethargy and oliguria or anuria at hospital admission.

The overall mortality rate of the present study was 19% and, interestingly, cats who died of a suspected ureteral or renal causes were not associated with complications or other parameters tested, suggesting that, the prognosis of cats after the renal decompression remains uncertain.

In summary, results of the present study suggest that SUB placement is a viable treatment of ureteral obstruction in cats, with fewer short and long-term complications when compared with ureteral *stents* or traditional ureteral surgery. Despite the difficulty to predict the patient outcome, prior and after to renal decompression, results of the present study show that cats with ureteral obstructions could have a good prognosis after a SUB device placement, when appropriately monitored.

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